ORIGINAL

THE HONORABLE JOHN C COUGHENOUR

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

TOM O'BRIEN and GUARDIANSHIP SERVICES OF SEATTLE, Guardian Ad Litem for DANIEL L TOPHAM, D D S , an incapacitated person, and CYNTHIA PAULEY-TOPHAM, D D S , individually and as wife of DANIEL L TOPHAM, and on behalf of their marital community,

Plaintiffs,

v

BAYER CORPORATION, a foreign corporation, SURVIVAL TECHNOLOGY, INC , a foreign corporation, MERIDIAN MEDICAL TECHNOLOGIES, INC , a foreign corporation, EM INDUSTRIES, INC , a foreign corporation, CENTER LABORATORIES, a Division of EM Industries, Inc , a foreign corporation, DEY LABORATORIES, INC , a foreign corporation,

Defendants

No C00-813C

MEMORANDUM IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT TO DISMISS PLAINTIFFS' STRICT LIABILITY CLAIMS RELATED TO THE EPIPEN

Note On Motion Calendar
June 8, 2001

ORAL ARGUMENT REQUESTED

I. INTRODUCTION/RELIEF REQUESTED

This is the second of two lawsuits brought by plaintiffs for damages arising out of an incident on July 31, 1997, when plaintiff Daniel L Topham, D D S allegedly sustained an allergic reaction to a bee sting The first case was filed in 1998 in King County Superior Court against, amongst others,

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

Daniel Topham's treating allergist, Dr Gail Shapiro In that medical malpractice action, plaintiffs alleged that Dr Shapiro, following allergy skin testing, informed Daniel Topham that he was not allergic to bee stings Daniel Topham sustained his July 31, 1997 bee sting less than a year after Dr Shapiro told him he was not allergic to bee stings and decided not to provide him with bee sting desensitization therapy

The instant case is a products liability action involving, in part, a medical product known as an EpiPen, which is an autoinjection device used by patients with certain allergies for the intramuscular injection of Epinephrine EpiPens are available only by prescription Epinephrine is used to treat allergic reactions Prior to his visit to Dr Shapiro, Daniel Topham had used EpiPens following bee stings Because she did not find him allergic to bee stings, Dr Shapiro did not prescribe any EpiPens to Daniel Topham In their previous case against Dr Shapiro, plaintiffs alleged that because of Dr Shapiro's misdiagnosis, Daniel Topham did not promptly use an EpiPen, and did not have a second one available — he gave his second EpiPen away and did not replace it because he thought he did not have a bee sting allergy Although plaintiffs allege that Daniel Topham used an EpiPen on July 31, 1997, no product used by him on that date has ever been produced Following the bee sting on July 31, 1997, Daniel Topham suffered a cardiac arrest and has brain damage

The parties in plaintiffs' prior suit against Dr Shapiro tried that case to a jury in the summer of 1999, and the jury found Dr Shapiro negligent and awarded plaintiffs damages of over $5 million [1] The parties settled that case at or around that time for the amount of the jury verdict

Following the Superior Court lawsuit, plaintiffs filed this second case in U S District Court seeking damages for the exact same injuries claimed in the first suit Defendants in this product liability action include among others, EM Industries, Inc ("EMI") and Center Laboratories, a

[1] The jury found Dr Shapiro negligent and awarded Dan Topham a total of $4,565,000 in past and future economic and non-economic damages, and awarded Cynthia Pauley Topham $500,000 in non-economic damages for loss of spousal consortium Thus, the total amount the jury awarded to both plaintiffs was $5,065,000

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

division of EM Industries, Inc ("Center"), the distributor of the EpiPen, and Meridian Medical Technologies, Inc — formerly Survival Technology, Inc ("Meridian/Survival"), the manufacturer of the EpiPen Plaintiffs have alleged various theories of liability, including strict liability under the Washington Products Liability Act

The undisputed facts set forth below show that (1) the EpiPen is a prescription-only medical product, to be lawfully prescribed only by licensed physicians, (2) there is no evidence that the subject EpiPen was defectively manufactured, and (3) the EpiPen is accompanied by physician instructions related to the use of the product, which are approved by the Food and Drug Administration ("FDA") Accordingly, under Washington Supreme Court jurisprudence, including Ruiz-Guzman v Amvac Chem , Corp , 141 Wn 2d 493, 7 P 3d 795 (2000) and Terhune v A H Robins Co , 90 Wn 2d 299, 577 P 2d 975 (1978), the EpiPen falls under the "unavoidably unsafe products" or "learned intermediary" exception, which bars certain strict liability claims under Washington law Accordingly, defendants request that this Court dismiss plaintiffs' strict liability claims against the defendant EpiPen manufacturer and distributor as a matter of law

II. UNDISPUTED FACTS

A. Procedural History.

Plaintiffs Daniel Topham, through a guardian ad litem, and Cynthia Pauley-Topham allege that on July 31, 1997, Dan Topham was stung by a yellow jacket bee while vacationing with his family in McCall, Idaho See First Amended Complaint for Damages [Product Liability], dated October 12, 2000, copy attached to Declaration of John S Devlin in Support of Motion for Partial Summary Judgment to Dismiss Strict Liability Claims Related to the EpiPen (21 U S C § 1746) ("Devlin Decl "), as Exhibit 1, at ¶ 2 10 Plaintiffs allege that Dr Topham suffered "severe and permanent brain damage and is unable to care for himself and is unable to return to his profession as a dentist " Id at ¶ 2 13

Previously, in 1998, plaintiffs Daniel Topham through a guardian ad litem, and Cynthia Pauley-Topham sued Dan Topham's allergist Gail G Shapiro, M D , her husband, and the

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

Northwest Asthma & Allergy Center, P S , alleging the exact same damages as in the instant case See Complaint [Professional Negligence], dated April 2, 1998, copy attached to Devlin Decl as Exhibit 2, at pp 2-3, ¶ III C In that lawsuit, plaintiffs alleged that on September 24, 1996, plaintiff Daniel Topham presented to Dr Shaprio for allergy testing and desensitization to yellow jackets, and "gave a history of anaphylactic reaction to yellow jacket stings " Id at p 2, ¶ III A Dr Shapiro's testing determined that he was not allergic to bee stings Id Plaintiffs alleged that on July 31, 1997, after suffering a yellow jacket sting, "[c]onsistent with Dr Shaprio's diagnosis and advice, Daniel did not immediately do anything after he was stung" and "shortly thereafter, Daniel experienced a severe anaphylactic reaction requiring CPR and hospitalization " Id at 2, ¶III B

On June 29, 1999, after a complete jury trial, the jury awarded plaintiffs $5,065,000, including $500,000 to plaintiff Cynthia Pauley-Topham See Special Verdict Form, dated June 29, 1999, copy attached to Devlin Decl as Exhibit 3

Plaintiffs' current lawsuit includes product liability claims against defendant Bayer Corporation — then the manufacturer of the product Dr Shaprio used to test and diagnose plaintiff Daniel Topham See Ex 1, at p 5, ¶3 1 1 Plaintiffs have also sued parties involved in the manufacture and distribution of the EpiPen, which plaintiffs now allege Daniel Topham used "shortly thereafter" his yellow jacket sting on July 31, 1997 Id at ¶2 1 1, 3 2 1-3 2 5 Plaintiffs' theories of liability include strict liability Id at ¶ 3 2 7

B. The EpiPen May Be Obtained only By Prescription From a Licensed Physician.

The EpiPen is an autoinjection device for the intramuscular administration of Epinephrine See Declaration of Gerald L Wannarka, Ph D , RAC (21 U S C § 1746), dated May 11, 2001 ("Wannarka Decl "), at ¶ 4 It is used to treat allergic reactions See Declaration of Peter Hauck in Support of Motion to Dismiss Plaintiffs' Strict Liability Claims Related to the EpiPen (21 U S C §1746) ("Hauck Decl "), at ¶ 3 The EpiPen is available only by prescription through lawfully licensed health care providers Wannarka Decl, at ¶ 6, Hauck Decl , at ¶3

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

C. There is No Evidence That the EpiPen Dan Topham Allegedly Used on July 31, 1997 Was Defectively Manufactured.

As an initial matter, plaintiffs have not produced the EpiPen they claim Dan Topham used on July 31, 1997, stating in response to defendants request for its production that "The Epi-Pen was left in the cabin at the time of the event, was not kept, and its eventual disposition is unknown." See Defendant Center Laboratories' First Discovery Requests Propounded to Plaintiffs with Plaintiffs' Responses, copy of excerpts attached to Devlin Decl as Exhibit 4, at 14 11-16

Plaintiffs have also produced no evidence that the EpiPen Dan Topham allegedly used was somehow defectively manufactured In response to an interrogatory specifically requesting that plaintiffs "State all facts supporting the allegation that the Epi-Pen (sic) 'was not reasonably safe as manufactured,'" Plaintiffs simply responded, "See answer to interrogatory No 11." Id at 15 14-17 However, "interrogatory No 11" requests facts supporting the allegation that the EpiPen is "not reasonably safe as designed" Id at 14 17-19 (emphasis added) In response to this interrogatory, plaintiffs failed to provide any facts or articulate a theory supporting a defective manufacture claim — or even a defective design claim — but instead stated allegations concerning the EpiPen's warnings None of the facts set forth in plaintiff's answers to interrogatories support a finding that the subject EpiPen was defectively manufactured

Further, since plaintiffs have not and, apparently, cannot produce the EpiPen Dan Topham allegedly used on July 31, 1997, it is impossible for them to prove that this particular EpiPen was defectively manufactured — in other words, that it was somehow improperly or defectively manufactured in such a way that it differed from or failed to perform in accordance with its intended design Indeed, Plaintiffs' discovery responses show that they cannot proffer any proof in this regard

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

D.

Are Approved by the Food & Drug Administration

The EpiPen is accompanied by physician warnings and prescribing instructions for both physicians and pharmacists Hauck Decl , at ¶ 4 In accordance with the Federal Food, Drug, and Cosmetic Act, 21 U S C §§ 301- 397, the EpiPen and its accompanying warnings underwent a multiyear evaluation and approval process by the FDA Wannarka Decl , at ¶ 5, Hauck Decl , at ¶ 4 The following is a summary of the FDA's approval process for the EpiPen New Drug Application ("NDA")

1. **1985 FDA Evaluation.** In 1985, Survival Technology, Inc submitted to the FDA an NDA for the EpiPen autoinjector, submitted "pursuant Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for EpiPen auto-injector (Epinephrine Injection)" See Correspondence, dated July 23, 1985, from Patricia H Russell, M D , Acting Director, Division of Surgical-Dental Drug Products, Office of Drug Research and Review, Center for Drugs and Biologics, Food & Drug Administration ("FDA") to Gary Leyland, Survival Technology, Inc ("Survival"), copy attached to Devin Decl as Exhibit 5 (Meridian 01752-53) The FDA reviewed Survival's labeling for the EpiPen — including warnings, precautions, and directions for use — and provided specific recommendations for changes in such labeling Id (Meridian 01752-53)

In response, Survival provided revised draft labeling for the EpiPen, incorporating the FDA's revisions and separating the EpiPen package inserts into two parts, entitled "PRESCRIBING INFORMATION" and "PATIENT INSTRUCTIONS " See Correspondence, dated August 26, 1985, from Gary W Leyland, Manager, Survival, to Patricia H Russell, M D , FDA, copy attached to Devlin Decl , as Exhibit 6 (Meridian 01755-01801) Survival specifically informed the FDA that the "patient will receive only the "PATIENT INSTRUCTIONS" and "in accordance with routine practice, the PRESCRIBING INFORMATION will be provided to physicians and to pharmacists " Id (capitalization and emphasis in original) In this correspondence, Survival specifically responded to the following comment contained in the FDA's July 23, 1985 correspondence

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

> We feel that the life-threatening aspect of anaphylaxis outweighs the concern about the drugs (sic) effect in certain types of patients i e those with heart disease or patients receiving certain types of drugs i e drugs which sensitize the heart We agree that epinephrine needs to be used more cautiously in these patients, but in the setting in which EpiPen and EpiPen Jr are proposed for use, there is no time for the patient to stop and assess the benefit risk aspects of administering the drug as is suggested under [Survival's proposed] Warnings and Precautions

Ex 5, at 1 In response to this FDA statement, Survival stated

> This comment reflects the fact that the current package insert contains patient instructions on the front and prescribing information on the back The judgment of risk versus benefit is not to be made by the patient at the time of proposed use Rather, it is intended for consideration by the physician before prescribing Based on the reviewers (sic) comment, we believe that there exists the possibility for confusion regarding the package insert which has been corrected
>
> We have separated the package insert into two parts PRESCRIBING INFORMATION AND PATIENT INSTRUCTIONS The patient will receive only the PATIENT INSTRUCTIONS In accordance with routine practice, the PRESCRIBING INFORMATION will be provided to physicians and pharmacists

See Ex 6, at Attachment A, ¶ 5 (Meridian 01765) (capitalization and emphasis in original)

On August 29, 1985, the FDA completed its "Medical Officer's Review," which approved the majority of Survival's August 26, 1985 labeling revisions, including Survival's decision to provide separate warnings for physicians and patients, stating "The sponsor [Survival] has responded to our concerns by dividing the package insert into two parts, one for the patient and one for the physician" See Medical Officer's Review, dated August 29, 1985, copy attached to Devlin Decl as Exhibit 7, at 1 In this regard, the FDA stated "this is acceptable, but we have further comments about these sections as noted below" Id The FDA's comments in this regard set forth certain changes to the physician labeling and the patient instructions for the EpiPen, including dosage administration instructions for physicians Id at 1-3

On September 16, 1985, Survival responded to the FDA's August 29, 1985 labeling modifications, and submitted its revised labeling for the EpiPen See Correspondence, dated September 16, 1985, from Gary W Leyland (Survival), to Patricia H Russell, M D (FDA), copy attached to Devlin Decl as Exhibit 8 (Meridian 01805-01840)

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

2. 1986 – 1987 FDA Evaluation, and Final FDA Approval of Product Labeling. Following Survival's September 1985 response, the FDA and Survival engaged in the evaluation and analysis of EpiPen largely unrelated to labeling

On January 27, 1987, Survival submitted another change to the EpiPen's labeling — both for the EpiPen's "Prescribing Information" and "EpiPen Patient Instructions." See Correspondence, dated January 27, 1987 from Gary W Leyland (Survival), to Patricia H Russell, M D (FDA), copy attached to Devlin Decl at Exhibit 9 (Meridian 01499-01533) Survival's submission included another complete set of instructions and warnings Id

On October 27, 1987, the FDA notified Survival that it had completed its review of Survival's new drug application, including Survival's various labeling and packaging submissions See Correspondence, dated October 27, 1987 from Paula Botstein, M D , Deputy Director (Medical Affairs), Office of Drug Research and Review, Center for Drug Evaluation and Research, FDA, copy attached to Devlin Decl as Exhibit 10 (Meridian 01545-01551) This correspondence stated that Survival's application was "approvable," but required some additional submissions, including draft labeling identical to the draft copies Survival submitted on January 27, 1987 with certain directed edits to portions of the "EpiPen Package Insert" and the "EpiPen and EpiPen Jr Patient Instructions" Id at 1-6 The FDA also required Survival to submit "advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign" Id at 6

On November 2, 1987, Survival complied with the FDA's October 27, 1987 request, specifically revising the EpiPen's labeling and the package insert and patient instructions See Correspondence, dated November 2, 1987, from Gary W Leyland (Survival), to Philip G Walters, M D , Director, Division of Surgical-Dental Products, Center for Drug Evaluation and Research, FDA, copy attached to Devlin Decl as Exhibit 11 (Meridian 01552-01606) On November 3, 1987, Survival submitted additional advertising material for the FDA's review See Correspondence, dated November 3, 1987, from Gary W Leyland (Survival), to FDA, Division of Drug Advertising and Labeling, copy attached to Devlin Decl as Exhibit 12 (Meridian 0612-0615)

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

On December 22, 1987, the FDA informed Survival that with regard to the EpiPen

> We have completed the review of this application, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate tha (sic) the drug product is safe and effective for use as recommended in the submitted draft labeling as revised below Accordingly, the application, with the labeling revisions described below, is approved effective as of the date of this letter

See Correspondence, dated December 22, 1987, from Paula Botstein, M D , Deputy Director (Medical Affairs), Office of Drug Research and Review, Center for Drug Evaluation and Research, FDA, to Gary Leyland (Survival), copy attached to Devlin Decl as Exhibit 13 (Meridian 01617-01618) The FDA prescribed six labeling revisions Id at 1-2

3. 1988 and 1989 FDA Evaluation. On May 17, 1988, Survival submitted to the FDA its final printed labeling materials to the FDA in response to the FDA's December 22, 1987 approval letter, including, among others (1) the EpiPen Immediate Container Label, (2) the EpiPen Patient Instructions, and (3) the EpiPen Physicians Insert See Correspondence, dated May 17, 1988 from Gary W Leyland (Survival), to Philip G Walter, M D (FDA), copy attached to Devlin Decl as Exhibit 14 (Meridian 01619-01629) The FDA acknowledged receipt of the final printed labeling "as requested in the [FDA's] approval letter for this application dated December 22, 1987 " See Correspondence, dated June 15, 1988, from Philip G Walters, M D (FDA), to Gary Leyland (Survival), copy attached to Devlin Decl as Exhibit 15 (Meridian 01632)

On September 6, 1988, the FDA requested that Survival amend its labeling to include additional warnings related to accidental EpiPen injection, and reiterating that the EpiPen should only be injected into thigh or upper arm See Correspondence, dated September 6, 1988, from Philip G Walters, M D (FDA) to Gary W Leyland (Survival), copy attached to Devlin Decl. as Exhibit 16 (Meridian 01642)

On February 13, 1989, Survival complied with the FDA's request, making changes to the Physicians' Inserts and Patients' Inserts See Correspondence, dated February 13, 1989 from Ianthana Peterson, Senior Regulatory Specialist (Survival) to Philip G Walters, M D (FDA), copy attached to Devlin Decl as Exhibit 17 (Meridian 01633-01641)

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

4. **1990 FDA Approval of Promotional Materials.** On March 2, 1989, the FDA approved Survival's February 13, 1989 labeling changes See Correspondence, dated March 2, 1989, from Philip G Walters, M D (FDA), to Ianthana Peterson (Survival), copy attached to Devlin Decl as Exhibit 18 (Meridian 01644)

On February 27, 1990, Survival submitted a revised draft of its proposed EpiPen autoinjector patient education brochure, containing changes reflecting comments made by the FDA's Mr William Pervis of the Division of Drug Advertising and Labeling See Correspondence, dated February 27, 1990, from Gary W Leyland (Survival), to Mr William Pervis, Division of Drug Advertising and Labeling, FDA, copy attached to Devlin Decl as Exhibit 19 (Meridian 01646-55) On March 2, 1990, the FDA approved these promotional materials, with specific revisions, stating

> The proposed material represents labeling for your product and will be referred to as promotional labeling to avoid confusion with the "approved" labeling The promotional labeling is intended to be used as a patient aid for your product and is set up in a "question/answer" format

See Correspondence, dated March 2, 1990, from William V Pervis (FDA), to Gary W Leyland (Survival), copy attached to Devlin Decl as Exhibit 20 (Meridian (01656-57) On September 9, 1991, Survival submitted its promotional labeling to the FDA with an official Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use See Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use, dated September 9, 1991, copy attached to Devlin Decl as Exhibit 21 (Meridian 1659-69)

III. ISSUE PRESENTED

Whether this Court should dismiss plaintiffs' strict liability claims when the undisputed material facts of this case show that (1) the EpiPen is a prescription-only medical product, (2) physicians authorized to prescribe EpiPens receive warnings and instructions concerning the prescribing of EpiPens, which are approved by the Food and Drug Administration, (3) there is no evidence — indeed, no allegation — that the physician warnings and instructions are insufficient, and (4) there is no evidence that the subject EpiPen was defectively manufactured

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

IV. EVIDENCE RELIED UPON

A. Declaration of John S Devlin in Support of Motion for Summary Judgment to Dismiss Plaintiffs' Strict Liability Claims Related to the EpiPen (21 U S C § 1746), and Exhibits 1 through 21, attached thereto

B. Declaration of Peter Hauck in Support of Motion to Dismiss Plaintiffs' Strict Liability Claims Related to the EpiPen (21 U S C § 1746)

C. Declaration of Gerald L Wannarka, Ph D, RAC (21 U S C § 1746)

V. MEMORANDUM OF AUTHORITIES

A.

The entry of summary judgment is appropriate when "there is no genuine issue of material fact" and "the moving party is entitled to judgment as a matter of law" Fed R Civ P 56, Celotex Corp v Catrett, 477 U S 317, 91 L Ed 2d 265, 106 S Ct 2548 (1986) Additionally, whether a fact is "material" is determined by the controlling substantive law Anderson v Liberty Lobby, Inc , 477 U S 242, 248, 91 L Ed 2d 202, 106 S Ct 2505 (1986) The moving party bears the responsibility of informing the District Court of the basis for its motion Celotex, 477 U S at 323 Moreover, such party must identify those portions of the pleadings, discovery papers and affidavits that demonstrate that no genuine issue of material fact exists Id

Once the moving party has satisfied these requirements, the burden then shifts to the nonmoving party to present affirmative evidence that a material fact is genuine and that an issue concerning that fact exists Summary Judgment will be entered against a party who fails to make showing sufficient to establish the existence of an element essential to the party's case, and on which that party has the ultimate burden of proof at trial Id at 323 Summary judgment is not defeated by any factual dispute, the issue must be genuine and material Liberty Lobby, 477 U S at 247-48 While the trial judge may not weight the evidence and determine the truth of the matter, "merely colorable" or "not significantly probative" evidence cannot prevent summary judgment Id

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

at 249-50 (citations omitted) Finally, a summary judgment may not be denied unless the evidence is such that a reasonable jury "might return a verdict" in the non-movant's favor Id at 257

B. Argument.

1. Washington Law Recognizes a Blanket Exception to Strict Liability for Prescription-Only Medical Products. Strict liability claims against the EpiPen — a prescription-only medical product — are precluded under Washington law because Washington courts recognize a blanket exception to strict liability for prescription-only medical products In a case the United States Court of Appeals for the Ninth Circuit certified to the Washington Supreme Court, Ruiz-Guzman v Amvac Chemical Corp , 141 Wn 2d 493, 7 P 3d 795 (2000), the Washington Supreme Court confirmed its long standing application of the "unavoidably unsafe product" or "Learned Intermediary" exception to the availability of the theory of strict liability[2] in Washington medical products liability cases Id at 505-509 As the Washington Supreme Court sated in Ruiz-Guzman, "There is no debate that this exception has been expressly adopted by this court " Id at 506 (citing Terhune v A H Robins Co , 90 Wn 2d 9, 12, 577 P 2d 975 (1978)) This exception to the application of strict liability is described in comment k to the Restatement (Second) of Torts, § 402A, as follows

> There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use These are especially common in the field of drugs Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician The seller of such products, again with *the qualification that they are properly prepared and marketed, and proper warning is* given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk

---

[2] Washington law accepts Section 402A of the Restatement (Second) of Torts, which establishes strict liability for "'[o]ne who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property '" Ruiz-Guzman, 141 Wn 2d at 505 (quoting Ulmer v Ford Motor Co , 75 Wn 2d 522, 530, 452 P 2d 729 (1969))

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

Ruiz-Guzman, 141 Wn 2d at 505-06 (quoting Restatement (Second) of Torts, § 402A cmt k (1969) and Terhune, 90 Wn 2d at 12) (emphasis added)

In Ruiz-Guzman, the Washington Supreme Court considered the question of whether the comment k exception could be applied to a pesticide Id at 505 The court determined that though comment k's "blanket exception" applies to "medical products," the exception does not apply to pesticides, which must be considered on a "product-by-product" basis Id at 511 In this regard, the Court specifically held "that the question of whether a pesticide is governed by comment k is to be determined on a product-by-product basis, as opposed to a blanket exemption like that for medical products "[3] (emphasis added) Id at 511 Thus, Washington law recognizes a blanket exception to strict liability for medical products

In its analysis, the Ruiz-Guzman court reviewed its prior application of the comment k exception in three medical product cases (1) Terhune v A H Robins Co , 90 Wn 2d 9, 577 P 2d 975 (1978), (2) Rogers v Miles Laboratories, 116 Wn 2d 195, 802 P 2d 1346 (1991), and (3) Young v Key Pharmaceuticals, Inc , 130 Wn 2d 160, 922 P 2d 59 (1996) Ruiz-Guzman, 141 Wn 2d at 506-07

In Terhune v A H Robins Co , the Court held that the manufacturers of a contraceptive device would not be liable for injuries caused by the product "if adequate warnings and instructions to prescribing physicians were supplied " Terhune, 90 Wn 2d at 13-14 In doing so, the Court

---

[3] In doing so, the court reasoned

> By its own terms, comment k is especially applicable to medical products The exceptions for medical products recognize the unique protection provided to the consumers of such products by the prescribing physician (and/or pharmacist) intermediary "[I]t [is] safe to surmise that ordinarily a physician will not prescribe or utilize a product which he does not consider reasonably safe, and that he will take into account the amount of testing, or lack thereof, which has been done with respect to the product " A physician possesses the medical training to assess adverse health effects of a medical product and to tailor that assessment to a particular patient As we noted in Terhune, the physician "is concerned with the total health and physical well being of his patients

Id at 508 (quoting Terhune, 90 Wn 2d at 16)

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

reasoned that, "[w]here the product is available only on prescription or through the services of a physician, the physician acts as a 'learned intermediary' between the manufacturer or seller and the patient" Id at 14 The Terhune court also stated

> It is [the physician's] duty to inform himself of the qualities and characteristics of those products which he prescribes for or administers to or uses on his patients, and to exercise an independent judgment, taking into account his knowledge of the patient as well as the product The patient is expected to and, it can be presumed, does place primary reliance upon that judgment The physician decides what facts should be told to the patient Thus, if the product is properly labeled and carries the necessary instructions and warnings to fully apprise the physician of the proper procedures for use and the dangers involved, the manufacturer may reasonably assume that the physician will exercise the informed judgment thereby gained in conjunction with his own independent learning, in the best interest of the patient

Id at 14 (emphasis added) The Court also stated that the principles of comment k "have their basis in the character of the medical profession and the relationship which exists between the manufacturer, the physician and the patient" Id at 16

The Washington Supreme Court's decision in Rogers v Miles Laboratories, 116 Wn 2d 195, 802 P 2d 1346 (1991), stands for the proposition that courts need not determine the adequacy of physician warnings in applying the comment k exception for strict liability when the subject product is a prescription-only medical product In Rogers, another medical product case certified by the Ninth Circuit to the Washington Supreme Court, the Court considered the issue of whether strict liability applied to a "for profit" pharmaceutical company for injuries allegedly resulting from its processing of HIV-contaminated blood products when it allegedly failed to adequately warn of the dangers of the product Id at 197 The Court determined that the comment k exception to strict liability applies to such products, stating in pertinent part

> Comment k justifies an exception from strict liability by focusing on the product and its relative value to society, rather than on the manufacturer's position in the stream of commerce Some products are necessary regardless of the risks involved to the user The alternative would be that a product, essential to sustain the life of some individuals, would not be available – thus resulting in a greater harm to the individual than that risked through use of the product

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

Id at 204

In Rogers v Miles Laboratories, the Court acknowledged the requirement associated with the comment k exception "that a manufacturer warn users of possible risks involved with its products in order to be free from liability" Id at 207 The Court also noted that comment k does not provide a definition for the phrase "proper warning," but confirmed its previous rule set forth in Terhune that the duty of the manufacturer of prescription products "to warn of dangers involved in use of a product is satisfied if he gives adequate warning to the physician who prescribes it" Id (quoting Terhune, 90 Wn 2d at 13) The Court also cited McKee v American Home Products, 113 Wn 2d 701, 782 P 2d 1045 (1989), which reiterated the Terhune "learned intermediary" doctrine — to wit, "a prescription drug manufacturer's duty to warn of dangers associated with its product runs only to the physician, it is the physician's duty to warn the ultimate consumer" McKee, 113 Wn 2d at 709

Relying on the comment k exception, the Rogers Court specifically ruled that the "proper tort standard" for a defendant manufacturer of the prescription-only medical product at issue "is that of negligence, not strict liability" Id at 208 In so ruling, the Court rejected the argument that "in order fully to resolve the question whether strict liability applies, we must also resolve whether defendants met their duty to warn under comment k" Id at 207 In this context, the Court agreed with a California Supreme Court decision, Brown v Superior Court, 44 Cal 3d 1049, 1059, 751 P 2d 470, 245 Cal Rptr 412 (1988), which reasoned that the failure-to-warn inquiry more properly invokes negligence tort theory rather than strict liability See Rogers, 116 Wn 2d at 207 (quoting Brown, 44 Cal 3d at 1059)[4] In this regard, the Washington Supreme Court stated "If the

[4] The Rogers court relied upon the following quote from the California Supreme Court's decision in Brown

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

manufacturer of an unavoidably unsafe product fails to provide an adequate warning, it has been negligent — but it is liable in negligence and not in strict liability" Id at 207

In Young v Key Pharmaceuticals, Inc, 130 Wn 2d 160, 922 P 2d 59 (1996), a plurality decision, the Washington Supreme Court affirmed the Court of Appeals' dismissal — based upon the comment k exception — of the plaintiff's strict liability claims against the manufacturer of a prescription asthma-relieving drug Id at 161-62, 164, 169 In doing so, the Court confirmed its ruling in Rogers, which "rejected the argument that, where a manufacturer has not met its duty to warn, it would be strictly liable" Id at 168 (citing Rogers, 116 Wn 2d at 207) In this regard, the Court stated that the "question whether [the defendant manufacturer] satisfied its duty to warn physicians of known dangers raises an issue of negligence, not strict liability" Id at 169 (emphasis added)

> In Young, the Court also ruled that comment k "applied to all prescription drugs," stating
>
> While there is language in comment k that can be read otherwise, the focus of both Terhune and Rogers is such that we conclude that a separate determination of whether a product is unavoidably unsafe need not be made on a case-by-case basis if that product is a prescription drug

Id at 170 (citing Rogers, 116 Wn 2d at 207, Terhune, 90 Wn 2d at 13-14,16) (emphasis added)

2. Strict Liability Claims Against the EpiPen Are Precluded Under Washington Law. As set forth above in Ruiz-Gusman, Terhune, Rogers, and Young, Washington law bars strict liability claims against manufacturers of prescription-only medical products accompanied by

---

> [T]here is a general consensus that, although [comment k] purports to explain the strict liability doctrine, in fact the principle it states is based upon negligence That is, comment k would impose liability on a drug manufacturer only if it failed to warn of a defect of which it either knew or should have known This concept focuses not on a deficiency in the product — the hallmark of strict liability — but on the fault of the producer in failing to warn of dangers inherent in the use of its product that were either known or knowable — an idea which "rings of negligence[ ] "

Brown, 44 Cal 3d at 1059 (quoting Cronin v J B E Olson Corp, 8 Cal 3d 121, 132, 501 P 2d 1153, 104 Cal Rptr 433 (1972))

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

warnings to the prescribing physician when there is no evidence that the product was defectively manufactured In the instant case, the EpiPen satisfies each of these conditions

a. It is Undisputed that the EpiPen is a Prescription-only Medical Product. In the instant case, the undisputed facts show that if indeed plaintiff Topham used an EpiPen on July 31, 1997, this item was a prescription-only medical product, which could only be properly prescribed by a duly licensed physician See Exs 5 through 21, Hauck Decl , at ¶¶ 3-4, Wannarka Decl , at ¶¶5-6 Plaintiffs cannot dispute this material fact

b. There is No Evidence That the EpiPen Dan Topham Allegedly Used on July 31, 1997 Was Defectively Manufactured. The Washington Products Liability Act specifically defines the conditions under which a defendant manufacturer may be liable for defective manufacturing or "construction" of a product

> A product is not reasonably safe in construction if, when the product left the control of the manufacturer, the product deviated in some material way from the design specifications or performance standards of the manufacturer, or deviated in some material way from otherwise identical units of the same product line

RCW 7 72 030(2)(a) Plaintiffs have no evidence to satisfy the requirements of RCW 7 72 030(2)(a) Plaintiffs have not proffered — nor can they — any evidence that the particular EpiPen Mr Topham allegedly used on July 31, 1997 was somehow defectively manufactured Simply, plaintiffs have no evidence that the subject EpiPen differed from its intended design due to some mistake or defect in the actual manufacturing process for that particular EpiPen

Plaintiffs have not produced the EpiPen they claim Dan Topham used on July 31, 1997, stating in response to defendants request for its production that "The Epi-Pen was left in the cabin at the time of the event, was not kept, and its eventual disposition is unknown " Ex 4, at 14 11-16

Plaintiffs have also produced no evidence that the EpiPen Dan Topham allegedly used was somehow defectively manufactured In response to an interrogatory specifically requesting that plaintiffs "State all facts supporting the allegation that the Epi-Pen (sic) 'was not reasonably safe as manufactured,'" Plaintiffs simply responded, "See answer to interrogatory No 11 " Id at 15 14-

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

17 However, "interrogatory No 11" requests facts supporting the allegation that the EpiPen is "not reasonably safe as designed" Id at 14 17-19 (emphasis added) In response to this interrogatory, plaintiffs failed to provide any facts or articulate a theory supporting a defective manufacture claim — or even a defective design claim — but instead stated allegations concerning the EpiPen's warnings None of the facts set forth in plaintiff's answers to interrogatories support a finding that the subject EpiPen was defectively manufactured There is no such evidence

c. **EpiPens are Accompanied by Physician Warnings.** The Federal Food, Drug, and Cosmetic Act specifically requires that an applicant submitting a New Drug Application submit "specimens of the labeling proposed to be used for such drug" 21 U S C § 355(b)(1)(F), Ben Venue Laboratories, Inc v Novartis Pharmaceutical Corp , 10 F Supp 2d 446, 448 (D N J 1998) There can be no dispute that EpiPens are distributed along with physician warnings and prescribing instructions See Hauck Decl , at ¶¶3-4, Wannarka Decl , at ¶¶5-6 There can be no dispute that the labeling and warnings accompanying EpiPens underwent a very extensive FDA approval process, with literally every word of such information – provided to both physicians and patients – carefully scrutinized by FDA reviewers See Exs 5-21

While Plaintiffs have alleged that the EpiPen's warnings are somehow defective, they do not allege that there are no warnings accompanying the EpiPen into the market With regard to prescription-only medical products such as the EpiPen, a manufacturer need only show that it provided warnings to the prescribing physician in order to avail itself of the comment k strict liability exception Here, there can be no dispute that the EpiPen has such warnings and instructions See Hauck Decl , at ¶4 The adequacy of such warnings is a negligence issue and strict liability does not apply

Based upon the undisputed facts, the comment k or "learned intermediary" exception applies to bar plaintiffs' claims against defendant as such claims relate to the EpiPen

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

VI. CONCLUSION

For the reasons set forth above, Defendants respectfully request that this Court dismiss with prejudice Plaintiffs' strict liability claims as they relate to the EpiPen

RESPECTFULLY SUBMITTED this 16TH day of MAY, 2001

LANE POWELL SPEARS LUBERSKY LLP

By _____
John S Devlin III, WSBA No 23988
Attorneys for Defendants EM Industries, Inc and
Center Laboratories, a Division of EM Industries, Inc

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

CERTIFICATE OF SERVICE

The undersigned declares under penalty of perjury that a true copy of this document was served via fax and overnight mail on counsel listed below at the locations listed below on the 16th day of May, 2001

Christopher L Otorowski, Esq
Morrow & Otorowski
298 Winslow Way West
Bainbridge Island, WA 98110-2510
Fax (206) 842-0797

Jeffrey R Johnson, Esq
Williams Kastner & Gibbs LLP
Two Union Square, Suite 4100
601 Union Ave
P O Box 21926
Seattle, WA 98111
Fax (206) 628-6611

Mr Douglas K Yoshida
Thorsrud Cane & Paulich
1350 Puget Sound Plaza
1325 Fourth Avenue
Seattle, WA 98101
Fax (206) 386-7795

Dated May 16, 2001 in Seattle, Washington

By _____
B Wilkins

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON, AT SEATTLE

TOM O'BRIEN and GUARDIANSHIP SERVICES OF SEATTLE, Guardian ad Litem for DANIEL L TOPHAM, DDS, an incapacitated person; and CYNTHIA PAULEY-TOPHAM, DDS, individually, and as wife of Daniel L. Topham, and on behalf of their marital community,

Plaintiffs,

v

BAYER CORPORATION, a foreign corporation; SURVIVAL TECHNOLOGY, INC , a foreign corporation; MERIDIAN MEDICAL TECHNOLOGIES, INC., a foreign corporation, EM INDUSTRIES, INC , a foreign corporation; CENTER LABORATORIES, a Division of EM INDUSTRIES, INC. a foreign corporation, and DEY LABORATORIES, INC , a foreign corporation,

Defendants

NO. C00-813C

FIRST AMENDED COMPLAINT FOR DAMAGES [PRODUCT LIABILITY]

COME NOW THE PLAINTIFFS, by and through their attorneys of record, Morrow & Otorowski, and for their causes of action against defendants allege as follows:

I. PARTIES AND JURISDICTION

1.1 Plaintiffs

1.1 1 Tom O'Brien And Guardianship Services Of Seattle, Guardian Ad Litem for Daniel L. Topham, DDS, An Incapacitated Person

At all times material hereto, the plaintiff Daniel L. Topham, DDS, the husband of Cynthia Pauley-Topham, was a resident of King County, Washington, and is currently a resident of the State of Utah. Daniel L. Topham, DDS, brings his causes of action individually and on behalf of his marital

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000; (206) 842-0797 FAX

community through his Guardian ad Litem, Tom O'Brien and Guardianship Services of Seattle. Tom O' Brien and Guardianship Services of Seattle, the court-appointed Guardian ad Litem for Daniel L. Topham, DDS, an incapacitated person, was authorized on December 17, 1999, in King County Cause No. 99-4-03640-6, to bring this products liability litigation on behalf of Daniel L. Topham, DDS.

1.1.2 Cynthia Pauley-Topham, DDS

At all times material hereto, the plaintiff, Cynthia Pauley-Topham, DDS, was the wife of Daniel L. Topham, DDS, and was and is a resident of King County, Washington. Cynthia Pauley-Topham, DDS, brings her causes of action individually and on behalf of her marital community

1.2 Defendants

1 2.1 Bayer Corporation

The defendant Bayer Corporation, ("Bayer"), is a foreign corporation transacting business in the State of Washington from at least 1996 to the present. The defendant Bayer is an Indiana corporation with its principal place of business in a state other than the State of Washington and to the plaintiffs' best information and belief, in the State of Connecticut. At all times material hereto, the defendant Bayer designed, manufactured, supplied, marketed, distributed and sold the product **Allergenic Extract Hymenoptera Venom** for diagnosis and hyposensitization of allergic reactions to insect stings

1.2 2 Survival Technology, Inc.

The defendant Survival Technologies, Inc., ("Survival"), at all times material hereto, was a foreign corporation transacting business in the State of Washington from at least 1969 to 1996. At all times material hereto, Survival was a Maryland corporation with its principal place of business in a state other than the State of Washington and to the plaintiffs' best information and belief, in the State of Maryland. At all times material hereto the defendant Survival designed, manufactured, supplied, marketed, distributed, and sold the product **Epi-Pen** to treat allergic reactions, including allergic reactions to insect stings.

1.2.3 Meridian Medical Technologies, Inc.

The defendant Meridian Medical Technologies, Inc , ("Meridian") is a foreign corporation

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

transacting business in the State of Washington from at least 1996 to the present. The defendant Meridian is a Maryland corporation with its principal place of business in a state other than the State of Washington and to the plaintiffs' best information and belief, in the State of Maryland At all times material hereto, the defendant Meridian designed, manufactured, supplied, marketed, distributed, and sold the product **Epi-Pen** to treat allergic reactions, including allergic reactions to insect stings.

1.2.4 EM Industries, Inc.

The defendant EM Industries, Inc., ("EM") is a foreign corporation transacting business in the State of Washington since at least 1996 to the present. The defendant EM is a New York corporation with its principal place of business in a state other than the State of Wasington and to the plaintiffs' best information and belief, in the State of New York At all times material hereto, the defendant EM designed, manufactured, supplied, marketed, distributed, and sold the product **Epi-Pen** to treat allergic reactions, including allergic reactions to insect stings.

1 2.5 Center Laboratories, A Division of EM Industries, Inc.

The defendant Center Laboratories, A Division of EM Industries, Inc , ("Center") is a foreign corporation transacting business in the State of Washington since at least 1996 to the present The defendant Center is a New York corporation with its principal place of business in a state other than the State of Washington and to the plaintiffs' best information and belief, in the State of New York At all times material hereto, the defendant Center designed, manufactured, supplied, marketed, distributed, and sold the product **Epi-Pen** to treat allergic reactions, including allergic reactions to insect stings.

1.2.6 Dey Laboratores, Inc.

The defendant Dey Laboratories, Inc , ("Dey") is a foreign corporation transacting business in the State of Washington from at least 1996 to the present. The defendant Dey is a California corporation with its principal place of business in a State other than the State of Washington and to plaintiffs' best information and belief in the State of California.

At all times material hereto, the defendant Dey designed, manufactured, supplied, marketed, distributed and sold the product **Epi-Pen** to treat allergic reactions, including allergic reactions

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

stings.

1.3 Jurisdiction

The plaintiff Daniel L Topham, an incapacitated person, is a resident of the State of Utah. The plaintiff Cynthia Pauley-Topham is a resident of the State of Washington

The defendants are each foreign corporations with their principle place of business outside the State of Washington No defendant in this lawsuit is a citizen of the same state as any plaintiff The amount in controversy in this litigation exceeds $75,000 00 This Court has jurisdiction pursuant to 28 U.S. Code § 1332. Pursuant to Local Rules W.D. Wash 5(e)(1), Seattle is the proper place of filing.

II. STATEMENT OF THE FACTS

2.1 In August of 1992, Daniel Topham was stung by a yellow jacket while playing golf in Utah. Daniel Topham was treated at a local emergency department for a serious systemic reaction and/or anaphylactic reaction to the yellow jacket sting and was given or prescribed an **Epi-Pen**

2.2 Thereafter, Daniel Topham carried an **Epi-Pen**.

2 3 On September 24, 1996, Daniel Topham presented to Gail Shapiro, M.D , an allergist at the Northwest Asthma & Allergy Center, P S., in Seattle, Washington.

2.4 Dr. Shapiro carried out skin testing for venom allergy on Daniel Topham.

2.5 The defendants' venom skin testing materials were used by Dr. Shapiro. The defendants' package insert for the venom skin testing materials states that the only approved method for diagnosing insect sting allergic patients for immunization is by skin testing The package insert did not warn about false negatives with venom skin testing; did not warn or inform that there were other methods of diagnosing patients with venom allergy; and did not warn or inform of the availability and need for immunization in particular categories of patients. Defendants failed to adequately and accurately inform users of necessary medical knowledge and research data applicable to their product.

2.6 The venom skin tests performed by Northwest Asthma & Allergy Center were recorded as negative.

2.7 The venom skin tests were negative.

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

2.8 Daniel Topham was not eligible for immunotherapy.

2.9 Daniel Topham did not receive venom immunotherapy.

2.10 On July 31, 1997, Daniel Topham was stung by a yellow jacket while vacationing with his family in McCall, Idaho.

2.11 Shortly thereafter, Daniel Topham did not feel well and injected the **Epi-Pen** into his thigh.

2.12 The **Epi-Pen** delivers a single 0 3 mg dose of Epinephrine A single 0.3 mg dose of Epinephrine is not adequate to treat a life-threatening anaphylactic reaction to an insect sting. The package insert does not warn that a single 0.3 mg dose of Epinephrine is not a life-saving dose of Epinephrine in a patient experiencing an anaphylactic reaction to an insect sting The package insert fails to warn and inform of the need for immediate administration of Epinephrine for patients with a history of anaphylactic reaction.

2.13 Daniel Topham suffered severe and permanent brain damage and is unable to care for himself and is unable to return to his profession as a dentist

III. LIABILITY AND PROXIMATE CAUSE

3.1 Claims Against Bayer Corporation

3.1.1 Bayer Corporation

At all times material hereto, the defendant Bayer was and is a product seller designing, manufacturing, supplying, marketing, distributing, and selling the product **Allergenic Extract Hymenoptera Venom** for diagnosis and hyposensitization of allergic reactions to insect stings. This is a products liability action and negligence action against the defendant Bayer brought pursuant to the laws of the State of Washington, to include RCW 7.72, *et seq* , and ordinary negligence. Plaintiffs hereby notify defendant that they are pleading all theories of recovery and bases for liability available pursuant to law to include negligence, strict liability, breach of express warranty, breach of implied warranty, inadequate warnings, misrepresentation and concealment of information, and violation of the Washington Consumer Protection Act.

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

3.1.2 Negligence

Defendant Bayer had a duty to the plaintiff, Daniel Topham, to manufacture, sell, ship, supply, and distribute the product **Allergenic Extract Hymenoptera Venom** reasonably safe and free from defects Defendant Bayer breached its duty by manufacturing, selling, shipping, supplying, and distributing the product **Allergenic Extract Hymenoptera Venom** that was defective, was not reasonably safe as manufactured, not reasonably safe because of inadequate warnings and because of failure to provide continuing warnings; by failing to exercise reasonable diligence, due care, and proper testing and monitoring of its product; by misrepresenting facts and concealing information, and by engaging in other negligent, careless and tortious conduct that will be set forth during discovery and trial As a direct and proximate result of defendant's breach of duties, the plaintiffs were severely and permanently injured.

3.1 3 Strict Liability

Defendant Bayer is strictly liable for plaintiffs' injuries for manufacturing, distributing, shipping, and selling the product **Allergenic Extract Hymenoptera Venom** that was defective, was not reasonably safe because of inadequate warnings and/or instructions, and was in a defective condition, which was unreasonably dangerous beyond the contemplation of an ordinary consumer at the time the product left the defendants' hands. When the product **Allergenic Extract Hymenoptera Venom** left the control of the defendant it was not reasonably safe, including but not limited to, defendant's failure to provide adequate warnings when it omitted that there were methods to diagnose insect sting allergies other than skin testing, failure to warn that the RAST test was available to diagnose insect sting allergies, failure to warn of the accuracy or inaccuracy of skin testing for insect sting allergies, failure to warn of the rate of false negatives in skin testing for insect sting allergies; failure to properly and adequately state the current medical knowledge and research data on patients' reactions to insect stings, including diagnosis, treatment, prognosis, testing, and the need to consider the severity of reactions; and the product **Allergenic Extract Hymenoptera Venom** was not reasonably safe to an extent beyond that which would be

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

contemplated by an ordinary consumer; and was a defective product.

3.1.4 Breach of Express and Implied Warranties

Defendant is liable for any breach of express and implied warranties, including but not limited to, the implied warranty of merchantability and fitness for a particular purpose made to the plaintiffs regarding its product.

3.1.5 Consumer Protection Act

Defendant is liable under the Consumer Protection Act, RCW 19.86, *et seq*., for unfair and deceptive acts and practices in the conduct of their trade and commerce.

3.2 Claims Against Survival Technology, Inc., Meridian Medical Technologies, Inc., EM Industries, Inc., Center Laboratories, a Division of EM Industries, Inc., and Dey Laboratories, Inc.

3.2.1 Survival Technology, Inc.

At all times material hereto, defendant Survival was and is a product seller designing, manufacturing, supplying, shipping, marketing, distributing, and selling the product **Epi-Pen** for treating allergic reactions, including allergic reactions to insect stings This is a products liability action and negligence action against the defendant Survival brought pursuant to the laws of the State of Washington, to include RCW 7 72, *et seq* , and ordinary negligence Plaintiffs hereby notify defendant that they are pleading all theories of recovery and bases for liability available pursuant to the law to include negligence, strict liability, breach of express warranty, breach of implied warranty, inadequate warnings, misrepresentation and concealment of information, and violation of the Washington Consumer Protection Act.

3.2.2 Meridian Medical Technologies, Inc.

At all times material hereto, defendant Meridian, was and is a product seller designing, manufacturing, supplying, shipping, marketing, distributing, and selling the product **Epi-Pen** for treating allergic reactions, including allergic reactions to insect stings. This is a products liability action and negligence action against the defendant Meridian brought pursuant to the laws of the State of Washington, to include RCW 7 72, *et seq*., and ordinary negligence. Plaintiffs hereby notify defendant

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

that they are pleading all theories of recovery and bases for liability available pursuant to the law to include negligence, strict liability, breach of express warranty, breach of implied warranty, inadequate warnings, misrepre-sentation and concealment of information, and violation of the Washington Consumer Protection Act.

3.2.3 EM Industries, Inc.

At all times material hereto, defendant EM Industries, Inc., was and is a product seller designing, manufacturing, supplying, shipping, marketing, distributing, and selling the product **Epi-Pen** for treating allergic reactions, including allergic reactions to insect stings. This is a products liability action and negligence action against the defendant EM Industries, Inc., brought pursuant to the laws of the State of Washington, to include RCW 7.72, *et seq.*, and ordinary negligence. Plaintiffs hereby notify defendant that they are pleading all theories of recovery and bases for liability available pursuant to the law to include negligence, strict liability, breach of express warranty, breach of implied warranty, inadequate warnings, misrepresentation and concealment of information, and violation of the Washington Consumer Protection Act.

3.2 4 Center Laboratories, a Division of EM Industries, Inc.

At all times material hereto, defendant Center Laboratories, a Division of EM Industries, Inc , was and is a product seller designing, manufacturing, supplying, shipping, marketing, distributing, and selling the product **Epi-Pen** for treating allergic reactions, including allergic reactions to insect stings. This is a products liability action and negligence action against the defendant Center Laboratories, a Division of EM Industries, Inc brought pursuant to the laws of the State of Washington, to include RCW 7.72, *et seq* , and ordinary negligence. Plaintiffs hereby notify defendant that they are pleading all theories of recovery and bases for liability available pursuant to the law to include negligence, strict liability, breach of express warranty, breach of implied warranty, inadequate warnings, misrepresentation and concealment of information, and violation of the Washington Consumer Protection Act.

3.2.5 Dey Laboratories, Inc.

At all times material hereto, defendant Dey was and is a product seller designing,

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

manufacturing, supplying, shipping, marketing, distributing, and selling the product **Epi-Pen** for treating allergic reactions, including allergic reactions to insect stings. This is products liability action and negligence action against the defendant Dey brought pursuant to the laws of the State of Washington to include RCW 7.72 *et seq* , and ordinary negligence. Plaintiffs hereby notify defendant that they are pleading all theories and bases for liability available pursuant to the law to include negligence, strict liability, breach of express warranty, breach of implied warranty, inadequate warnings, misrepresentation and concealment of information, and violation of the Washington Consumer Protection Act.

3.2.6 Negligence

Defendants, and each of them, had a duty to the plaintiff, Daniel Topham, to design, manufacture, sell, ship, supply, and distribute the product **Epi-Pen** that was reasonably safe and free from defects. Defendants, and each of them, breached their duty by designing, manufacturing, selling, shipping, and distributing the product **Epi-Pen** which was defective, was not reasonably safe as designed, was not reasonably safe as manufactured, was not reasonably safe because of inadequate warnings, was not reasonably safe because of failure to provide continuing warnings, was not reasonably safe because of failure to exercise reasonable diligence, due care, proper testing and monitoring of its product, by misrepresenting facts and concealing information; and by engaging in other negligent, careless and tortious conduct that will be set forth during discovery and trial. As a direct and proximate result of defendants' breach of duties, the plaintiffs were severely and permanently injured

3.2.7 Strict Liability

Defendants are strictly liable for plaintiffs' injuries for designing, manufacturing, distributing, shipping, supplying and selling the product **Epi-Pen** that was defective in design, was not reasonably safe because of inadequate warnings and/or instructions, was defective and unsafe because the likelihood that the product **Epi-Pen** would fail and cause plaintiffs' harm, or similar harm to other people, and the seriousness of those harms outweighed the burden on these defendants to design and manufacture an **Epi-Pen** that would have prevented those harms, and the **Epi-Pen** was in a defective condition which was unreasonably dangerous beyond the contemplation of an ordinary consumer at the time the product

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

left the defendants' hands. When the product **Epi-Pen** left the control of the defendants, it was not reasonably safe, including but not limited to, the design of the **Epi-Pen** for a single 0.3 mg. dose of Epinephrine, which is not a life-saving dose of Epinephrine; the product as designed and sold provided a single 0.3 mg dose of Epinephrine, which is not adequate to treat a life-threatening anaphylactic reaction to an insect sting; the defendants failed to warn that the single 0.3 mg. dose of Epinephrine is not a life-saving dose of Epinephrine for allergic emergencies (anaphylaxis); failed to warn that a patient with a history of a prior anaphylactic reaction to an insect sting should immediately administer the **Epi-Pen**; failed to provide continuing warnings; the **Epi-Pen** was unsafe for use in the foreseeable circumstances and conditions that existed when the plaintiff was injured; and defendants misrepresented facts and concealed information and otherwise placed an unsafe product into the stream of commerce.

3.2.8 Breach of Express and Implied Warranties

Defendants are liable for breach of all express and implied warranties, including but not limited to, the implied warranty of merchantability and fitness for the particular purpose made by plaintiff of its product.

3.2.9 Consumer Protection Act

Defendants are liable under the Consumer Protection Act, RCW 19.86, *et seq.*, for unfair and deceptive acts and practices in the conduct of their trade and commerce.

IV. DAMAGES

4.1 As a direct and proximate result of defendants' negligence and breach of duties; the defective and unsafe design and manufacture and failure to warn under strict liability; breach of express and implied warranties; and violation of the Consumer Protection Act, Daniel Topham, DDS, has been severely and permanently injured and damaged. Damages include medical expenses, past and future; severe and permanent impairment of Daniel Topham's ability and capacity to enjoy life, past and future; emotional distress, past and future; impairment of wage earning capacity and economic loss past and future; and damages pursuant to RCW 19.86, *et.seq.*, all in an amount to be proven at the time of trial as reasonable and proper as determined by a trier of fact

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000; (206) 842-0797 FAX

4.2 As a direct and proximate result of defendants' negligence and breach of duties; the defective and unsafe design and manufacture and failure to warn under strict liability; the breach of express and implied warranties; and violation of the Consumer Protection Act to the plaintiff, Daniel Topham, DDS, the plaintiff, Cynthia Pauley-Topham, DDS, has been severely and permanently injured and damaged. Damages include loss of marital consortium, economic loss, and emotional distress, all in an amount to be proven at the time of trial as reasonable and proper as determined by a trier of fact.

V. PRAYER FOR RELIEF

WHEREFORE, plaintiffs pray for judgment against defendants Bayer Corporation, Survival Technology, Inc., Meridian Medical Technologies, Inc , EM Industries, Inc., Center Laboratories, a Division of EM Industries, Inc , and Dey Laboraties, Inc., in such sum or sums as shall be determined at trial, plus statutory costs and attorney fees, incidental and consequential damages, treble damages, and reasonable attorney fees under the Washington Consumer Protection Act, and for such other relief as the court shall deem just and proper.

VI. LIMITED WAIVER OF PHYSICIAN-PATIENT PRIVILEGE

Pursuant to RCW 5 60.060(4)(b), plaintiffs hereby waive the physician-patient privilege only insofar as necessary to place any and all alleged damages at issue at the time of trial, as might be required by statute or amended statute or case law interpreting the statutes of the State of Washington. It should be understood that plaintiffs' actions do not constitute a waiver of any of the plaintiffs' constitutional rights and that the defendants are not to contact any treating physician, past, present, or subsequent, without first notifying counsel for plaintiffs so that they might bring the matter to the attention of the Court and seek appropriate relief by imposing limitations and restrictions upon the defendants to contact past, present, or

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000; (206) 842-0797 FAX

subsequent treating physicians *ex parte* pursuant to the rule announced in Louden v. Mhyre, 110 Wn 2d 675 (1988).

DATED this 12th day of October, 2000.

MORROW & OTOROWSKI

By: _____
Albert Morrow, WSBA #5880
Of Attorneys for Plaintiffs

MORROW & OTOROWSKI, LLP
ATTORNEYS AT LAW
298 WINSLOW WAY WEST
BAINBRIDGE ISLAND, WASHINGTON 98110
(206) 842-1000, (206) 842-0797 FAX

FILE COPY

IN THE SUPERIOR COURT OF THE STATE OF WASHINGTON
IN AND FOR THE COUNTY OF KING

CYNTHIA PAULEY-TOPHAM, DDS., as Guardian ad Litem for DANIEL L. TOPHAM, DDS., an incapacitated person; and CYNTHIA PAULEY-TOPHAM, DDS., and DANIEL L. TOPHAM, DDS., individually and as husband and wife,

Plaintiffs,

v.

GAIL G. SHAPIRO, M.D., individually; GAIL G. SHAPIRO, M.D., and PETER A. SHAPIRO, DDS., as husband and wife; and NORTHWEST ALLERGY & ASTHMA CENTER, P.S.

Defendants.

NO. 98-2-08621-1SEA

COMPLAINT
[PROFESSIONAL NEGLIGENCE]

COME NOW plaintiffs, by and through their attorneys of record, Morrow & Otorowski, and for their causes of action against the defendants allege as follows:

I. IDENTIFICATION OF PLAINTIFFS

The plaintiffs, Daniel L.Topham, DDS., and Cynthia Pauley-Topham, DDS., are husband and wife and at all times material hereto were residents of King County, Washington. The plaintiffs, Daniel L. Topham and Cynthia Pauley-Topham, bring this action in furtherance of their individual rights and as husband and wife on behalf of their marital community. The plaintiff, Daniel L. Topham, who has suffered severe mental and physical injuries rendering him incompetent of managing his property or caring for himself, brings his causes of action through his Guardian Ad Litem, Cynthia Pauley-Topham.

////

////

MORROW & OTOROWSKI, LLP
Attorneys at Law
298 Winslow Way West
Bainbridge Island, Washington 98110
206-842-1000, 206-842-0797 Fax

II. IDENTIFICATION OF DEFENDANTS

A. Gail G. Shapiro, M.D.

At all times material hereto, the defendant, Gail G. Shapiro, M.D., was a licensed physician specializing in allergy and immunology, practicing in the State of Washington, including Seattle, King County, Washington. At all times material hereto, there existed a fiduciary health care provider/patient relationship between the defendant Gail G. Shapiro, M.D., and the plaintiff Daniel L. Topham.

B. Gail G. Shapiro, M.D., and Peter A. Shapiro, DDS.

At all times material hereto, the defendants Gail G. Shapiro, M.D., and Peter A. Shapiro, DDS., were husband and wife, residing in King County, Washington.

C. Northwest Asthma & Allergy Center, P.S.

The defendant Northwest Asthma & Allergy Center, P.S., is a professional corporation licensed in the State of Washington and all times material hereto, employed various agents and employees, including Gail G. Shapiro, M.D., who rendered medical care and treatment to the plaintiff Daniel L. Topham, as set forth in the Statement of Facts herein.

III. STATEMENT OF THE FACTS

A. On September 24, 1996, the plaintiff Daniel L. Topham, presented to the defendant Gail G. Shapiro, M.D., at the Northwest Allergy & Asthma Center, P.S., for allergy testing and desensitization to yellow jackets. Daniel gave a history of anaphylactic reaction to yellow jacket stings. Dr. Shapiro carried out testing on Daniel and determined he was not allergic to bee stings. Dr. Shapiro charted that Daniel had "no venom allergy" and that there were "no special recommendations."

B. On July 31, 1997, the plaintiff Daniel L. Topham was stung by a yellow jacket while vacationing with his family in McCall, Idaho. Consistent with Dr. Shapiro's diagnosis and advice, Daniel did not immediately do anything after he was stung. Shortly thereafter, Daniel experienced a severe anaphylactic reaction requiring CPR and hospitalization.

C. Daniel has suffered severe and permanent brain damage and is unable to care for himself

MORROW & OTOROWSKI, LLP
Attorneys at Law
298 Winslow Way West
Bainbridge Island, Washington 98110
206-842-1000, 206-842-0797 Fax

and is unable to return to his profession as a dentist.

IV. LIABILITY AND NEGLIGENCE

A. This is an action for professional negligence and malpractice against the defendants brought pursuant to the laws of the State of Washington, to include RCW 7.70, *et seq.*, and ordinary negligence. Plaintiffs hereby notify the defendants they are pleading all theories of recovery and bases of liability available pursuant to law to include negligence, lack of informed consent, and negligent failure to appropriately evaluate, monitor, refer, treat, diagnose, intervene, test, advise, and otherwise render the necessary care their patient required.

B. As a direct and proximate result of the fiduciary health care provider/patient relationship that existed between the defendants and the plaintiff, Daniel L. Topham, the defendants owed the duty to provide reasonably prudent medical care, including but not limited to properly diagnosing and treating Daniel L. Topham's bee sting allergy. During the course of their relationship, the defendants breached their duty owed to Daniel L. Topham by failing to properly diagnose and treat Daniel L.Topham's bee sting allergy, by failing to refer Daniel L. Topham to specialized allergy care providers, and by failing to inform the plaintiffs of the material risks associated with their approach to treatment. The direct and proximate result of the defendants' failure to provide reasonably prudent medical care was that the plaintiffs suffered the severe and permanent injury herein later described.

V. DAMAGES

As a direct and proximate result of defendants' negligence and breach of duties, Daniel L. Topham and his wife Cynthia Pauley-Topham have been severely and permanently injured and damaged. Damages include medical expenses, past and future; loss of wages, past and future; severe and permanent impairment of Daniel L. Topham's ability and capacity to enjoy life, past and future; serious and permanent impairment of spousal consortium; all in an amount to be proven at the time of trial as reasonable and proper as determined by a trier of fact.

////

////

MORROW & OTOROWSKI, LLP
Attorneys at Law
298 Winslow Way West
Bainbridge Island, Washington 98110
206-842-1000; 206-842-0797 Fax

VI. LIMITED WAIVER OF PHYSICIAN/PATIENT PRIVILEGE

Pursuant to RCW 5.60.060(4)(b) plaintiffs hereby waive the physician/patient privilege only insofar as is necessary to place any and all alleged damages at issue at the time of trial, as might be required by statute or amended statute or case law interpreting the statutes of the State of Washington. It should be understood that plaintiffs' actions do not constitute a waiver of any of the plaintiffs' constitutional rights and that the defendants are not to contact any treating physician, past, present, or subsequent, without first notifying counsel for plaintiffs so that they might bring the matter to the attention of the Court and seek appropriate relief in terms of imposing limitations and restrictions upon any desire or intent by the defendants to contact past or subsequent treating physicians *ex parte* pursuant to the rule announced in Louden v. Mhyre, 110 Wn.2d 675 (1988).

WHEREFORE, plaintiffs pray for judgment against the defendants, and each of them, by way of damages in such an amount as might be proven at the time of trial and decided and determined by a trier of fact as reasonable and just under the evidence, as well as for costs and disbursements herein incurred, and for such further relief as the Court may deem just and equitable.

DATED this 21 day of April, 1998.

MORROW & OTOROWSKI

By: _____

Christopher L. Otorowski, WSBA #8248
Albert Morrow, WSBA #5880
Carol N. Johnston, WSBA #25425
Attorneys for Plaintiffs

MORROW & OTOROWSKI, LLP
Attorneys at Law
298 Winslow Way West
Bainbridge Island, Washington 98110
206-842-1000, 206-842-0797 Fax

IN THE SUPERIOR COURT OF THE STATE OF WASHINGTON

IN AND FOR THE COUNTY OF KING

CYNTHIA PAULEY-TOPHAM, D.D.S., as Guardian ad Litem for DANIEL L. TOPHAM, D.D.S., an incapacitated person; and CYNTHIA PAULEY-TOPHAM, D.D.S., and DANIEL L. TOPHAM, D.D.S., individually and as husband and wife, Plaintiffs, v. GAIL G. SHAPIRO, M.D., individually; GAIL G. SHAPIRO, M.D., and PETER A. SHAPIRO, D.D.S., as husband and wife; and NORTHWEST ALLERGY & ASTHMA CENTER, P.S. Defendants.	NO. 98-2-08621-1SEA **SPECIAL VERDICT FORM**

We, the jury, make the following answers to the questions submitted by the court:

QUESTION No. 1: Were any of the following negligent?

Answer "yes" or "no" after the name of each defendant.

Answer:		**Yes**	**No**
Defendant:	Gail Shapiro, M.D.	✓	
Defendant:	Northwest Asthma & Allergy Center, P.S.		✓

If you answer Question No. 1 "no" as to each defendant, sign and return this verdict. If you answer Question No. 1 "yes" as to any defendant, then answer Question No. 2.

QUESTION No. 2: Was such negligence a proximate cause of injury to Daniel Topham?

Answer "yes" or "no" after the name of each defendant found negligent by you in Question No. 1.

Answer:	**Yes**	**No**
Defendant: Gail Shapiro, M.D	✓	____
Defendant: Northwest Asthma & Allergy Center, P.S.	____	____

If you answer Question No. 2 "no" as to all defendants, sign and return this verdict. If you answer Question No. 2 "yes" as to any defendant, answer Question No. 3.

QUESTION NO. 3: What do you find to be the plaintiffs' amount of damages?

Answer (a) Past Economic Damages of Daniel Topham:	$ $165,000
Answer (b) Future Economic Damages of Daniel Topham:	$ 3,400,000
Answer (c) Non-Economic Damages of Daniel Topham:	$ 500,000
Answer (d) Non-Economic Damages of Cynthia Topham:	$ 500,000

If you answer Question No. 3 with any amount of money, answer Question No. 4. If you find no damages, sign and return this verdict.

QUESTION NO. 4. Assume that 100 % represents the total combined negligence which proximately caused the plaintiffs' damage. What percentage of this 100% is attributable to each defendant whose negligence was found by you in Question No. 2 to have been a proximate cause of the damage to the plaintiffs? (Your total must equal 100%.)

Answer:	**Percentage**
Defendant: Gail Shapiro, M.D.	100
Defendant: Northwest Asthma & Allergy Center, P.S.	ϕ
TOTAL	100%

Sign and return this verdict.

Dated. June 29, 1999 Foreperson: Brenda Houston

THE HONORABLE JOHN C COUGHENOUR

CERTIFICATE OF SERVICE
The undersigned declares under penalty of perjury that a true copy of this document was served on via overnight delivery service on Christopher Morrow, at 296 Winslow Way West Bainbridge Island, WA 98110, on the 29th day of December, 2000 Dated this same day in Seattle, Washington

By_____
B Wilkins

I hereby certify under penalty of perjury under the laws of the State of Washington that on this day I mailed a copy/original of the document to which this Certificate is attached, via U.S. Mail, postage prepaid/Federal Express, to: J. JOHNSON (COPY) · D. YOSHIDA (REV) J. DEVLIN (ORIGINAL)
3-30-01 BAINBRIDGE IS WA
Date and Place
Certified By Elaine M. Grace

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

TOM O'BRIEN and GUARDIANSHIP SERVICES OF SEATTLE, Guardian Ad Litem for DANIEL L TOPHAM, D D.S., an incapacitated person, and CYNTHIA PAULEY-TOPHAM, D D S , individually and as wife of DANIEL L TOPHAM, and on behalf of their marital community,

Plaintiffs,

v.

BAYER CORPORATION, a foreign corporation, SURVIVAL TECHNOLOGY, INC., a foreign corporation; MERIDIAN MEDICAL TECHNOLOGIES, INC , a foreign corporation, EM INDUSTRIES, INC , a foreign corporation, CENTER LABORATORIES, a Division of EM Industries, Inc , a foreign corporation, DEY LABORATORIES, INC , a foreign corporation,

Defendants

No C00-813C

DEFENDANT CENTER LABORATORIES' FIRST DISCOVERY REQUESTS PROPOUNDED TO PLAINTIFFS

WITH PLAINTIFFS' RESPONSES

TO: Plaintiffs, above-named,

AND TO: Morrow & Otorowski, LLP, Plaintiffs' Counsel

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101

ORIGINAL

REQUEST FOR PRODUCTION NO. 8: Produce all documents, records, and texts or other references that support, evidence or relate to the allegation contained in Paragraph 2.12 of the First Amended Complaint that "[a] single 0.3 mg dose of Epinephrine is not adequate to treat a life-threatening anaphylactic reaction to an insect sting."

RESPONSE:

OBJECTION Overbroad, unduly burdensome, and cumulative. Notwithstanding the objection, Physicians Desk Reference's brochure, obtained from Center Laboratories, and within defendant's possession, reveals that the "Usual epinephrine adult does for allergic emergencies is 0 3 mg, " and, "With severe persistent anaphylaxis, repeat injections with an additional Epi-Pen may be necessary."

REQUEST FOR PRODUCTION NO. 9 Please produce the Epi-Pen which plaintiffs allege in Paragraph 2 11 of the First Amended Complaint that Daniel Topham injected into his thigh on July 31, 1997

RESPONSE:

The Epi-Pen was left in the cabin at the time of the event, was not kept, and its eventual disposition is unknown

INTERROGATORY NO 11: State all facts supporting the allegation in Paragraph 3 2 6 of the First Amended Complaint that the Epi-Pen "was not reasonable safe as designed."

ANSWER:

The PDR package insert, provided from Center Laboratories, reveals that with severe persistent anaphylaxis, repeat injections with an additional Epi-Pen may be necessary. The patient package insert, provided from Center Laboratories, fails to reveal that with severe persistent anaphylaxis, repeat injections with an additional Epi-Pen may be necessary. The unknowing patient therefore cannot trust that the Epi-Pen, as designed, will safely help him survive an anaphylactic reaction. The Epi-Pen, as designed, fails to be reasonably safe in that a patient may need more than

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101

one dose to survive an anaphylactic reaction, yet a patient may not realize the need to have an additional Epi-Pen immediately available for use.

INTERROGATORY NO 12. Identify all persons who have knowledge of the facts supporting the allegation in Paragraph 3.2 6 of the First Amended Complaint that the Epi-Pen "was not reasonably safe as designed."

ANSWER:

Other than employees of defendant, Center, see response to interrogatory no 2

REQUEST FOR PRODUCTION NO. 10: Please produce all documents, records, texts, and other references supporting the allegation in Paragraph 3.2.6 of the First Amended Complaint that the Epi-Pen "was not reasonably safe as designed."

RESPONSE:

Other than the body of medical literature that generally discusses epinephrine, plaintiff is unaware of any other documents, records, texts, or other references

INTERROGATORY NO. 13: State all facts supporting the allegation in Paragraph 3.2 6 of the First Amended Complaint that the Epi-Pen "was not reasonable safe as manufactured."

ANSWER:

See answer to interrogatory no. 11.

INTERROGATORY NO. 14: Identify all persons who have knowledge of the facts supporting the allegation in Paragraph 3.2.6 of the First Amended Complaint that the Epi-Pen "was not reasonably safe as manufactured."

ANSWER:

See response to interrogatory no. 12

REQUEST FOR PRODUCTION NO 11: Please produce all documents, records, and references supporting the allegation in Paragraph 3.2.6 of the First Amended Complaint that the Epi-Pen "was not reasonably safe as manufactured."

ATTORNEY'S CR 26 CERTIFICATION

The undersigned attorney certifies pursuant to Civil Rule 26(g) that he or she has read each response and objection to these discovery requests, and that to the best of his or her knowledge, information, and belief formed after a reasonable inquiry, each is (1) consistent with the Civil Rules and warranted by existing law or a good faith argument for the extension, modification, or reversal of existing law, (2) not interposed for any improper purpose, such as to harass or to cause unnecessary delay or needless increase in the costs of litigation, and (3) not unreasonable or unduly burdensome or expensive, given the needs of the case, the discovery already had in the case, the amount in controversy, and the importance of the issues at stake in the litigation

DATED at _____, Washington, this _____ day of _____, 2000

MORROW & OTOROWSKI, LLP

By _____
Albert Morrow, WSBA #5880
Attorneys for Plaintiffs

VERIFICATION

I declare under penalty of perjury under the laws of the State of Washington that I am CYNTHIA PAULEY, _____ of _____, Guardian ad Litem for plaintiff Dan Topham herein, am authorized to make this statement, have read the foregoing responses to Defendant Center's First Discovery Requests, know the contents thereof, and believe them to be true and correct

DATED at Bellevue, WA, this 3RD day of May, 2000

By Cynthia Pauley
Printed/typed Name

STATE OF WASHINGTON)
) ss
COUNTY OF KING)

I certify that I know or have satisfactory evidence that CYNTHIA PAULEY is the person who appeared before me, and said person acknowledged that _____ signed this instrument and acknowledged it to be {his/her} free and voluntary act for the uses and purposes mentioned in this instrument

DATED May 2, 2001

Elaine Greene

ELAINE M GREENE NOTARY PUBLIC STATE OF WASHINGTON COMMISSION EXPIRES 1-29-02

Print Name ELAINE GREENE
NOTARY PUBLIC for the State of Washington, residing at
BAINBRIDGE ISLAND WA
My appointment expires 1/29/02

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

ATTORNEY'S CR 26 CERTIFICATION

The undersigned attorney certifies pursuant to Civil Rule 26(g) that he or she has read each response and objection to these discovery requests, and that to the best of his or her knowledge, information, and belief formed after a reasonable inquiry, each is (1) consistent with the Civil Rules and warranted by existing law or a good faith argument for the extension, modification, or reversal of existing law, (2) not interposed for any improper purpose, such as to harass or to cause unnecessary delay or needless increase in the costs of litigation; and (3) not unreasonable or unduly burdensome or expensive, given the needs of the case, the discovery already had in the case, the amount in controversy, and the importance of the issues at stake in the litigation.

DATED at _____, Washington, this _____ day of _____, 2000

MORROW & OTOROWSKI, LLP

By: _____
Albert Morrow, WSBA #5880
Attorneys for Plaintiffs

VERIFICATION

I declare under penalty of perjury under the laws of the State of Washington that I am Tom O'Brien Executive Director, of Guardianship Services, Plaintiffs herein, am authorized to make this statement, have read the foregoing responses to Defendant Center's First Discovery Requests, know the contents thereof, and believe them to be true and correct.

DATED at Seattle, WA, this 3rd day of May, 2001 ~~2000~~.

By. Tom O'Brien
Printed/typed Name. Tom O'Brien

STATE OF WASHINGTON)
) ss.
COUNTY OF King)

I certify that I know or have satisfactory evidence that Tom O'Brien is the person who appeared before me, and said person acknowledged that he signed this instrument and acknowledged it to be ~~his/her~~ free and voluntary act for the uses and purposes mentioned in this instrument.

DATED 3 May, 2001

Ann R. Menzel

Print Name ANN R. MENZEL
NOTARY PUBLIC for the State of Washington, residing at ~~Seattle~~

My appointment expires: JAN 13, 2002

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101
(206) 223-7000

ATTORNEY'S CR 26 CERTIFICATION

The undersigned attorney certifies pursuant to Civil Rule 26(g) that he or she has read each response and objection to these discovery requests, and that to the best of his or her knowledge, information, and belief formed after a reasonable inquiry, each is (1) consistent with the Civil Rules and warranted by existing law or a good faith argument for the extension, modification, or reversal of existing law, (2) not interposed for any improper purpose, such as to harass or to cause unnecessary delay or needless increase in the costs of litigation; and (3) not unreasonable or unduly burdensome or expensive, given the needs of the case, the discovery already had in the case, the amount in controversy, and the importance of the issues at stake in the litigation.

DATED at Bainbridge Island, Washington, this 30th day of March, 2001

MORROW & OTOROWSKI, LLP

By: _____
Christopher L. Otorowski WSBA # 8248
Attorneys for Plaintiffs

VERIFICATION

I declare under penalty of perjury under the laws of the State of Washington that I am CHRISTOPHER L. OTOROWSKI, OF ATTORNEYS FOR, Plaintiffs herein, am authorized to make this statement, have read the foregoing responses to Defendant Center's First Discovery Requests, know the contents thereof, and believe them to be true and correct.

DATED at BAINBRIDGE ISLAND, this 30TH day of MARCH, 2001.

By: _____
Printed/typed Name: CHRIS OTOROWSKI

STATE OF WASHINGTON)
) ss
COUNTY OF KITSAP)

I certify that I know or have satisfactory evidence that CHRIS OTOROWSKI is the person who appeared before me, and said person acknowledged that HE signed this instrument and acknowledged it to be {his/her} free and voluntary act for the uses and purposes mentioned in this instrument.

DATED: MARCH 30, 2001

Elaine M. Greene

Print Name ELAINE M. GREENE
NOTARY PUBLIC for the State of Washington, residing at BAINBRIDGE IS

My appointment expires 1/29/02

ELAINE M GREENE NOTARY PUBLIC STATE OF WASHINGTON

LANE POWELL SPEARS LUBERSKY LLP
SUITE 4100
1420 FIFTH AVENUE
SEATTLE, WA 98101

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430

JUL 26 1985

Survival Technology Inc.
8101 Glenbrook Road
Bethesda, MD 20814

CONFIDENTIAL

JUL 2 3

GWL 7/26

cc: E. Bartnee
D. Baum
C. Caskie
N. Crank
S. Becker
S. Everett
G. Homan
D. Brassink
N. Monroe
R. James
Dr. Spinelli

Attention: Gary Leyland

Gentlemen:

Please refer to your pending new drug application dated January 31, 1985 submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for EpiPen Auto-Injector (epinephrine injection).

We also acknowledge receipt of your additional communications dated April 29 and June 18, 1985 amending the application.

We have completed a review of the clinical section of the NDA and have the following recommendations for changes in the labeling for both EpiPen and EpiPen Jr.:

1. Under Directions for Use, what is now step 2 should precede what is now step 1. That is "place black tip on outer thigh" should precede "pull out gray safety cap." We feel that the medication could be lost by inadvertently brushing against the black tip if the safety cap has been removed.

2. Under Contraindications, please comment on whether you feel that patients with organic brain damage should not receive epinephrine to treat life-threatening anaphylaxis.

3. Under Warnings, please comment on whether you feel there is any danger associated with the use of discolored epinephrine. If not, we still feel that patients should be alerted to the fact that discoloration may represent oxidation and loss of potency of the medication.

4. The statements "Do not inject into buttock" and "Do not inject intravenously" should be capitalized in the Warnings section.

5. We feel that the life-threatening aspect of anaphylaxis outweighs the concern about the drugs effect in certain types of patients i.e. those with heart disease or patients receiving certain types of drugs i.e. drugs which sensitize the heart. We agree that epinephrine needs to be used more cautiously in these patients, but in the setting in which EpiPen and EpiPen Jr. are proposed for use, there is no time for the patients to stop and assess the benefit:risk aspects of administering the drug as is suggested under Warnings and Precautions.

CONFIDENTIAL

6. In the Dosage and Administration section, we feel that the detail in the first paragraph is unnecessary. There is only one dose that will be administered regardless of the patient's weight and the patient should not be given the medication unless there is a risk of anaphylaxis.

7. In regard to the How Supplied section, the statement that "Package containing one EpiPen Auto-Injector and in packages of six units" is confusing and should be clarified.

Please submit revised draft labeling within 30 days of your receipt of this letter or as soon as possible.

Sincerely yours,

Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Survival Technology, Inc.

August 26, 1985

CONFIDENTIAL

NDA 19-430
Patricia H. Russell, M.D.
Director
Division of Surgical-Dental Drug Products
Room 18B-08 HFN160
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Russell:

Please refer to our new drug application for the EpiPen and EpiPen Jr. Auto-Injector (epinephrine injection), NDA 19-430, and to your letter dated July 23, 1985, concerning this application. The letter provided recommendations for changes in the labeling for both EpiPen and EpiPen Jr.

Our responses to the labeling recommendations are enclosed in Attachment A. The revised draft labeling is enclosed in Attachment B. The revised labeling incorporates the suggested wording and format agreed to by your staff and Survival Technology at a meeting held on July 5, 1985.

We have separated the package insert into two parts: PRESCRIBING INFORMATION and PATIENT INSTRUCTIONS. The patient will receive only the PATIENT INSTRUCTIONS. In accordance with routine practice, the PRESCRIBING INFORMATION will be provided to physicians and pharmacists.

Please feel free to call me at (301) 656-5600 if you have any questions.

Sincerely,

Gary W. Leyland

Gary W. Leyland
Manager
Clinical and Regulatory Affairs

GWL/sle
ATTACHMENTS

MERIDIAN
01755

8101 GLENBROOK ROAD • BETHESDA MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892694 • CABLE SURTECH, BHDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN 106)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

Form Approved OMB No 0910-0001

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21 Code of Federal Regulations, § 314 1)

NOTE No person shall introduce or deliver for introduction into interstate commerce any new drug unless approval of an application filed pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act has been approved with respect to such drug.

Name of applicant SURVIVAL TECHNOLOGY, INC. CONFIDENTIAL

Address 8101 Glenbrook Road Bethesda, MD 20814

Date August 26, 1985 Telephone (301) 656-5600

Name of new drug EpiPen & EpiPen Jr. Auto-Injectors (epinephrine injection)

- ☐ Original application (regulation § 314 1)
- ☒ Amendment to original, unapproved application (regulation § 314 6)
- ☐ Abbreviated application (regulation § 314 1(f))
- ☐ Amendment to abbreviated unapproved application (regulation § 314 6)
- ☐ Supplement to an approved application (regulation § 314 8)
- ☐ Amendment to supplement to an approved application

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application, and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §201 100 (21 CFR 201 100) It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §314 8 of the new-drug regulations

Attached hereto, submitted in the form described in §314 1(e) of the new-drug regulations, and constituting a part of this application are the following

1 **Table of contents** The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any)

2 **Summary** A summary demonstrating that the application is well-organized adequately tabulated statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested The summary should include the following information (In lieu of the outline described below and the evaluation described in Item 3 and expanded summary and evaluation as outlined in §314 1(d) of the new drug regulations may be submitted to facilitate the review of this application)

a Chemistry

i Chemical structural formula or description for any new drug substance

ii Relationship to other chemically or pharmacologically related drugs

iii Description of dosage form and quantitative composition

b Scientific rationale and purpose the drug is to serve

c Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice new-drug application or master file of which any contents are being incorprated by reference to support this application

d Preclinical studies (Present all findings including all adverse experiences which may be interpreted as incidental or not drug related Refer to date and page number of the investigational drug notice(s) or the volume and page number of this applictation where complete data and reports appear)

i Pharmacology (pharmacodynamics endocrinology metabolism etc)

ii Toxicology and pathology Acute toxicity studies subacute and chronic toxicity studies reproduction and teratology studies miscellaneous studies

e Clinical studies (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found)

i Special studies not described elsewhere

ii Dose range studies

iii Controlled clinical studies

iv Other clinical studies (for example uncontrolled or incompletely controlled studies)

v Clinical laboratory studies related to effectiveness

vi Clinical laboratory studies related to safety

vii Summary of literature and unpublished reports available to the applicant

3 **Evaluation of safety and effectiveness** a Summarize separately the favorable and unfavorable evidence for each claim in the package labeling Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found

b Include tabulation of all side effects or adverse experience by age sex and dosage formulation whether or not considered to be significant showing whether administration of the drug was stopped and showing the investigator s name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found Indicate those side effects or adverse experiences considered to be drug related

4 **Copies of the label and all other labeling to be used for the drug** (a total of 12 copies if in final printed form 4 copies if in draft form)

a Each label or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies the market package

b If the drug is to be offered over the counter labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed recommended or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it the application should also contain labeling that includes adequate information for all such uses including all the purposes for which the over the counter drug is to be advertised to or represented for use by physicians

c If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended including all the purposes for which it is to be advertised or represented in accord with §201 100 (21 CFR 201 100) The application should include any labeling for the drug intended to be made available to the layman

d If no established name exists for a new-drug substance the application shall propose a nonproprietary name for use as the established name of for the substance

e Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug

f No application may be approved if the labeling is false or misleading in any particular

When mailing pieces any other labeling or advertising copy are devised for promotion of the new drug samples shall be submitted at the time of initial placement of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §310 300 of the new drug regulations) Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application

g If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its label shall bear a statement directed to the pharmacist specifying the type(s) of container(s) to be used in dispensing the drug to maintain its identity strength quality and purity so as to be in conformance with the provisions of §201 100(b)

5 A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it

6 A full list of the articles used as components of the drug This list should include all substances used in the synthesis extraction or other method of preparation of any new drug substance and in the preparation of the finished dosage form regardless of whether they undergo chemical change or are removed in the process Each substance should be identified by its established name if any or complete chemical name using structural formulas when necessary for specific identification If any proprietary preparation is used as a component the proprietary name should be followed by a complete quantitative statement of composition Reasonable alternatives for any listed substance may be specified

7 A full statement of the composition of the drug The statement shall set forth the name and amount of each ingredient whether active or not contained in a stated quantity of the drug in the form in which it is to be distributed (for example amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form All components should be included in the batch formula regardless of whether they appear in the finished product Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown Reasonable variations may be specified

8 A full description of the methods used in and the facilities and controls used for the manufacture processing and packing of drug Included in this description should be full information with respect to any new-drug substance and to the new drug dosage form as follows in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture processing and packing and the described facilities and controls to determine and preserve the identity strength quality and purity of the drug

a A description of the physical facilities including building and equipment used in manufacturing processing packaging labeling storage and control operations

b A description of the qualifications including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety identity strength quality and purity it purports or is represented to possess and a statement of their responsibilities

c The methods used in the synthesis extraction isolation or purification of any new drug substance When the specifications and control applied to such substance are inadequate in themselves to determine its identity strength quality and purity the methods should be described in sufficient detail including quantities used times temperatures pH solvents etc, to determine these characteristics Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified

d Precautions to assure proper, identity strength quality and purity of the raw materials whether active or not including the specifications for acceptance and methods of testing for each lot of raw material

e Whether or not each lot of raw materials is given a serial number to identify it and the use made of such numbers in subsequent plant operations

f If the applicant does not himself perform all the manufacturing processing packaging labeling and control operations for any new-drug substance or the new drug dosage form his statement identifying each person who will perform any part of such operations and designating the part and a signed statement from each such person fully describing directly or by reference the methods facilities and controls in his part of the operation

g Method of preparation of the master formula records and individual batch records and manner in which these records are used

h The instructions used in the manufacturing processing packaging and labeling of each dosage form of the new drug including any special precautions observed in the operations

i Adequate information with respect to the characteristics of and the test methods employed for the container closure or other component parts of the drug package to assure their suitability for the intended use

j Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug

k Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and if so at what stage and by whom it is done

l Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield This should include a description of the accounting for such items as discards breakage etc and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy

m Precautions to assure that each lot of the drug is packaged with the proper label and labeling including provisions for labeling storage and inventory control

n The analytical controls used during the various stages of the manufacturing processing packaging and labeling of the drug including a detailed description of the collection of samples and the analytical procedures to which they are subjected The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components If the article is one that is represented to be sterile the same information with regard to the manufacturing processing packaging and the collection of samples of the drug should be given for sterility controls Include the standards used for acceptance of each lot of the finished drug

o An explanation of the exact significance of the batch control numbers used in the manufacturing processing packaging and labeling of the drug including the control numbers that appear on the label of the finished article State whether these numbers enable determination of the complete manufacturing history of the product Describe any methods used to permit determination of the distribution of any batch if its recall is required

p A complete description of and data derived from studies of the

stability of the drug, including information showing the suitability of the analytical method used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new drug substance for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple dose container and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

g. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product. (An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9 Samples of the drug and articles used as components, as follows: *a* The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays.

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance as defined in §310.3(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial scale production batch, and a representative sample or samples of each new drug substance as defined in §310.3(g) of the new-drug regulations, from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new drug substance and other assayed components of the finished drug. *Provided, however*, That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with name of the applicant and the new drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to item 9a, a statement of the additional samples that will be submitted as soon as available, and, with respect to each sample submitted, full information with respect to its identity, the origin of any new drug substance contained therein (including, in the case of new-drug substances, a statement whether it was produced on a laboratory pilot-plant or full production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include, for any reference standard, a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the National Center for Drugs and Biologics and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10 Full reports of preclinical investigations that have been made to show whether or not the drug is safe and effective for use. *a* An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child bearing potential.

c. Detailed reports of any pertinent microbiological and in vitro studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11 List of investigators. *a* A complete list of all investigators supplied with the drug, including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant or submitted to him by an investigator or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12 Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. *a* An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects designed to record observations and permit evaluation of any and all discernable effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FDA 1639, Drug Experience Report (obtainable with instructions on request from the

Food and Drug Administration, Department of HHS 5600 Fishers Lane, Rockville, Maryland 20857), for each adverse experience or, if feasible for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FDA-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c In lieu of a FDA Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion, all formats proposed for such use will require initial review and approval by the Food and Drug Administration

e All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted Reprints are not required of reports in designated journals, listed in §310 9 of the new-drug regulations, about related drugs, a bibliography will suffice Include the evaluation of the safety or effectiveness of the drug that has been made by the applicant s medical department, expert committee or consultants

f If the drug is a combination of previously investigated or marketed drugs an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications and ineffectiveness in use of such components Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration

g The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity strength quality and purity if it differs from the description in Item 6 7 or 8 of the application

h In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320 Subpart B)

13 If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application

Observe the provisions of §314 8 of the new-drug regulations concerning supplemental applications

14 [Reserved]

15 The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §25 1 of this chapter

16 Nonclinical Laboratory Studies — With respect to each nonclinical laboratory study contained in the application either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in part 58 of this chapter or if the study was not conducted in compliance with such regulations a statement that describes in detail all differences between the practices used in the study and those required in the regulations

17 Conduct Of Clinical Investigations — Statements contained in the application regarding each clinical investigation involving human subjects, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter areas not subject to such requirements in accordance with §§56 104 or 56 105 and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter

CONFIDENTIAL

Signature of Applicant	Per *(Responsible official or agent)* Gary W. Leyland
Gary W. Leyland	Indicate authority Manager Clinical & Regulatory Affairs — Telephone (301) 656-5600

(Warning: A willfully false statement is a criminal offense U S C Title 18, sec 1001)

Note. This application must be signed by the applicant or by an authorized attorney, agent, or official If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States

CONFIDENTIAL

ATTACHMENT A

RESPONSES TO MEDICAL REVIEWERS COMMENTS

CONFIDENTIAL

1. Under Directions for Use, what is now step 2 should precede what is now step 1. That is "place black tip on outer thigh" should precede "pull out gray safty cap." We feel that the medication could be lost by inadvertently brushing against the black tip if the safety cap has been removed.

Our records do not reveal accidental activation of the auto-injector by brushing against the black tip to be a problem. The auto-injector is designed to activate when a force of 2-8 lbs., is axially applied to the front end (black tip). Brushing against the black tip connotes a radial rather than an axial force of less than 2 lbs., which is not sufficient to activate the auto-injector.

We believe that changing the instructions might cause a significant amount of confusion for physicians, nurses, pharmacists and patients familiar with the current instructions for use. Based on our discussion with Dr. Niklas, we will try to obtain information from physicians and nurses who have knowledge of actual EpiPen usage by patients to determine if a problem exists. We will consider changing the instructions if a problem is identified.

CONFIDENTIAL

2. Under Contraindications, please comment on whether you feel that patients with organic brain damage should not receive epinephrine to treat life-threatening anaphylaxis.

We have concluded that there are no absolute contraindications to the use of epinephrine in a life-threatening situation. Accordingly, we have deleted organic brain damage from the Contraindications section.

CONFIDENTIAL

3. Under Warnings, please comment on whether you feel there is any danger associated with the use of discolored epinephrine. If not, we still feel that patients should be alerted to the fact that discoloration may represent oxidation and loss of potency of the medication.

We performed a MEDLINE search of the scientific literature from 1966 through 1984 using epinephrine toxicology as the search heading. A review of the titles, abstracts and select articles did not reveal any reference to toxicity associated with the use of discolored epinephrine. We agree that discoloration of the epinephrine solution may represent oxidation and loss of potency.

The USP monograph for Epinephrine Injection contains the statement "Do not use the Injection if it is brown or contains a precipitate". This matter was discussed with Drs. Russell and Niklas at our July 5 meeting. They recommended that we change the label statement to read, "Replace if solution is brown or discolored", or words to that effect. This recommendation is based on their conclusion that in a life-threatening situation, it is better to receive potentially sub-potent epinephrine than no epinephrine at all. We feel that an EpiPen Auto-Injector should be replaced if the solution is discolored and have included words to that effect on the label, prescribing information, and patient instructions.

CONFIDENTIAL

4. The statements "Do no inject into buttock" and "Do not inject intravenously" should be capitalized in the Warnings section.

The statements "DO NOT INJECT INTO BUTTOCK" and "DO NOT INJECT INTRAVENOUSLY" are now capitalized in the Warnings section.

CONFIDENTIAL

5. We feel that the life-threatening aspect of anaphylaxis outweights the concern about the drugs effect in certain types of patients i.e. those with heart disease or patients receiving certain types of drugs i.e. drugs which sensitize the heart. We agree that epinephrine needs to be used more cautiously in these patients, but in the setting in which EpiPen and EpiPen Jr. are proposed for use, there is no time for the patients to stop and assess the benefit:risk aspects of administering the drug as is suggested under Warnings and Precautions.

This comment reflects the fact that the current package insert contains patient instructions on the front and prescribing information on the back. The judgement of risk versus benefit is not to be made by the patient at the time of proposed use. Rather, it is intended for consideration by the physician before prescribing. Based on the reviewers comment, we believe that there exists the possibility for confusion regarding the package insert which has been corrected.

We have separated the package insert into two parts: *PRESCRIBING INFORMATION AND PATIENT* INSTRUCTIONS. The patient will receive only the PATIENT INSTRUCTIONS. In accordance with routine practice, the PRESCRIBING INFORMATION will be provided to physicians and pharmacists.

CONFIDENTIAL

6. In the Dosage and Administration section, we feel that the detail in the first paragraph is unnecessary. There is only one dose that will be administered regardless of the patient's weight and the patient should not be given the medication unless there is a risk of anaphylaxis.

We feel that full prescribing information must be available to the physician prior to his recommending the EpiPen Auto-Injector to his patients. There is dosage flexibility with EpiPen in increments of 0.15 mg epinephrine by combining the EpiPen and EpiPen Jr., if the physician thinks such precision is important for his patient. We have added the following statement to allow for dosage flexibility: "Dosage may be individualized by use of EpiPen and EpiPen Jr. in combination".

CONFIDENTIAL

7. In regard to the How Supplied section, the statement that "Package containing one EpiPen Auto-Injector and in packages of six units" is confusing and should be clarified.

We have revised the above statement to read, "EpiPen Auto-Injectors (Epinephrine Injection, USP, 1:1000, 0.3ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0301-01".

CONFIDENTIAL

ATTACHMENT B

1. EPIPEN PRESCRIBING INFORMATION
2. EPIPEN JR. PRESCRIBING INFORMATION

3. EPIPEN PATIENT INSTRUCTIONS
4. EPIPEN JR. PATIENT INSTRUCTIONS

5. EPIPEN LABEL
6. EPIPEN JR. LABEL

CONFIDENTIAL

1. EPIPEN PRESCRIBING INFORMATION

CONFIDENTIAL

EPIPEN 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

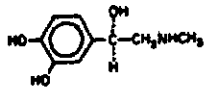
Delivers 0.3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:1,000 (0.3 ml).

DESCRIPTION

The EpiPen Auto-Injector provides epinephrine for emergency intramuscular injection. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 ml) in a sterile solution. Each 0.3 ml contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection.

Epinephrine is a sympathomimetic catecholamine.

Chemically epinephrine is β-(3,4-dihydroxyphenyl) -α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to hymenoptera stings, foods, drugs and other allergens. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, thereby relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to hymenoptera stings, foods, drugs and other allergens. The EpiPen Auto-Injector is intended for immediate self-administration by individuals with a history of anaphylactic reactions. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59 F-86 F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selec-

tion of an injection site such as the thig.
DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine should be administered with extreme caution to patients who have developed degenerative heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency. The physician must balance these warnings against the potentially life-saving role of emergency epinephrine.

PRECAUTIONS

The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium l-thyroxine.

Administer with caution to hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals,

pregnant women, and children under 30kg (66lbs.) body weight. For emergency use, a careful benefit-risk judgement may be necessary.

Use of this product may be inadvisable for patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its ingredients.

ADVERSE REACTIONS

Transient and minor side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessnes, tenseness, anxiety, and fear.

Ventricular arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician should review with the patient, in detail, the patient instructions and operation of the EpiPen Auto-Injector. Inject the delivered dose of the EpiPen Auto-Injector (0.3 ml Epinephrine

Injection, USP, 1:1,000) intramuscularly into the anterolateral aspect of the thigh. See detailed Directions for Use on the accompanying Patient Instructions.

Dosage in any specific patient should be based on body weight in addition to the patient's risk of anaphylaxis and ability to tolerate epinephrine. Usual epinephrine adult dose for allergic emergencies is 0.3 mg. Usual pediatric dose is 0.01 mg/kg body weight. Dosage may be individualized by use of EpiPen and EpiPen Jr. in combination.

Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection, USP, 1:1,000, 0.3 ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0301-01. Store in a dark place at room temperature (59 F-86 F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue August 1985

Manufactured for Center Laboratories, Division of EM Industries, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

CONFIDENTIAL

CONFIDENTIAL

2. EPIPEN JR. PRESCRIBING INFORMATION

CONFIDENTIAL

EPIPEN Jr. 0.15 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

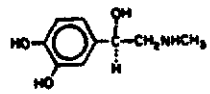
Delivers 0.15 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:2,000 (0.3 ml).

DESCRIPTION

The EpiPen Jr. Auto-Injector provides epinephrine for emergency intramuscular injection. Each EpiPen delivers a single dose of 0.15 mg epinephrine from Epinephrine Injection, USP, 1:2,000 (0.3 ml) in a sterile solution. Each 0.3 ml contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection.

Epinephrine is a sympathomimetic catecholamine.

Chemically, epinephrine is β-(3,4 dihydroxyphenyl) -α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to hymenoptera stings, foods, drugs and other allergens. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, thereby relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to hymenoptera stings, foods, drugs and other allergens. The EpiPen Auto-Injector is intended for immediate self-administration by individuals with a history of anaphylactic reactions. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59 F-86 F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selection of an injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral

hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine should be administered with extreme caution to patients who have developed degenerative heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency. The physician must balance these warnings against the potentially life-saving role of emergency epinephrine.

PRECAUTIONS

The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium l-thyroxine.

Administer with caution to hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30kg (66lbs.) body weight. For emergency use, a careful benefit-risk judgement may be necessary.

Use of this product may be inadvisable for patients who have previously demonstrated an

acute hypersensitivity reaction on injection of any of its ingredients.

ADVERSE REACTIONS

Transient and minor side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessnes, tenseness, anxiety, and fear.

Ventricular arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr. should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician should review with the patient, in detail, the patient instructions and operation of the EpiPen Jr. Auto-Injector. Inject the delivered dose of the EpiPen Jr. Auto-Injector (0.3 ml Epinephrine Injection, USP, 1:2,000) intramuscularly into the anterolateral aspect of the thigh. See detailed Directions for Use on the accompanying Patient Instructions.

Dosage in any specific patient should be based on body weight in addition to the

patient's risk of anaphylaxis and ability to tolerate epinephrine. Usual epinephrine dose for allergic emergencies is 0.01mg/kg body weight in pediatric patients.

Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

EpiPen Jr. Auto-Injectors (Epinephrine Injection, USP, 1:2,000, 0.3 ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0302-01. Store in a dark place at room temperature (59 F-86 F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue August 1985

Manufactured for Center Laboratories, Division of EM Industries, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

3. EPIPEN PATIENT INSTRUCTIONS

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,

BEFORE AN EMERGENCY ARISES

LOT NO.

NDC 0268-0301-01

DIN 509558

EPIPEN

NSN 6305-01-152-7626

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.3 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:1,000(0.3 ml)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (59 F-86 F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Industries, Inc., Port Washington, NY 11050, U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814 U.S.A.

US Patent No 3,882,863 and 4,031,893

MERIDIAN
01785

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Auto-Injector should be used only by hypersensitive (allergic) individuals in the event of an allergic emergency as prescribed by a physician.

THE EPIPEN AUTO-INJECTOR

The EpiPen Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.3 mg of epinephrine.

*Keep the EpiPen Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Auto Injector is designed with a see through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF INSECT STING ALLERGY

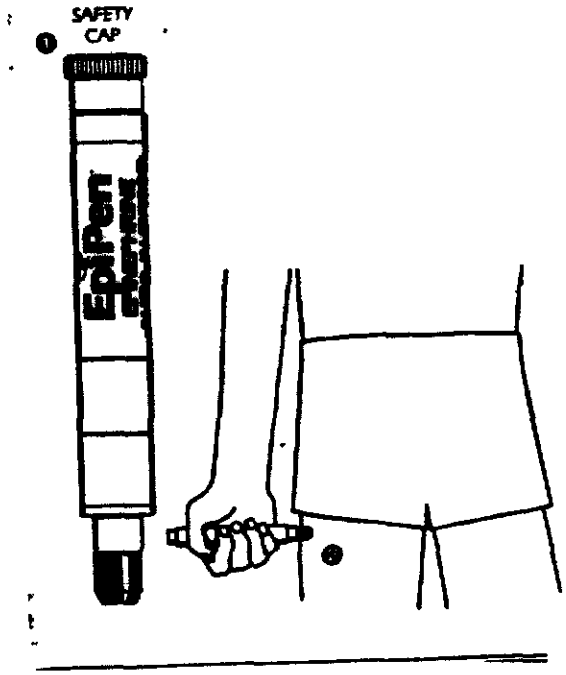
If you have been stung by an insect and experience the signs and symptoms described by your physician, use the EpiPen Auto-Injector immediately. If possible, remove the insect's stinger with your fingernails; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen , be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

Before using, check to make sure solution in Auto-Injector is not brown in color. (Replace if discolored) Then follow these directions:

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Apply to thigh regardless of what part of the body has been stung.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



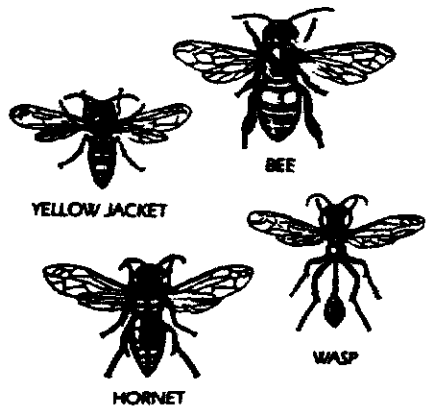
ADDITIONAL PATIENT INFORMATION

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



CONFIDENTIAL

Tear off here and mail to address shown at bottom

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers a free EpiPen® Auto-Injector Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories,
EpiPen Alert,
35 Channel Drive,
Port Washington, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____ (Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

6.
MERIDIAN
01790

CONFIDENTIAL

4. EPIPEN JR. PATIENT INSTRUCTIONS

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,

BEFORE AN EMERGENCY ARISES

LOT NO.

CONFIDENTIAL

NDC 0268-0302-01

DIN 509558

EPIPEN JR.

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:2,000(0.3 ml)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (59 F-86 F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of *EM Industries, Inc., Port Washington, NY 11050,* U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814 U.S.A.

MERIDIAN 01792

US Patent No 3,882,863 and 4,031,893

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Jr. Auto-Injector should be used only by hypersensitive (allergic) individuals in the event of an allergic emergency as prescribed by a physician.

THE EPIPEN JR. AUTO-INJECTOR

The EpiPen Jr. Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.15 mg of epinephrine.

*Keep the EpiPen Jr. Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Jr. Auto Injector is designed with a see through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF INSECT STING ALLERGY

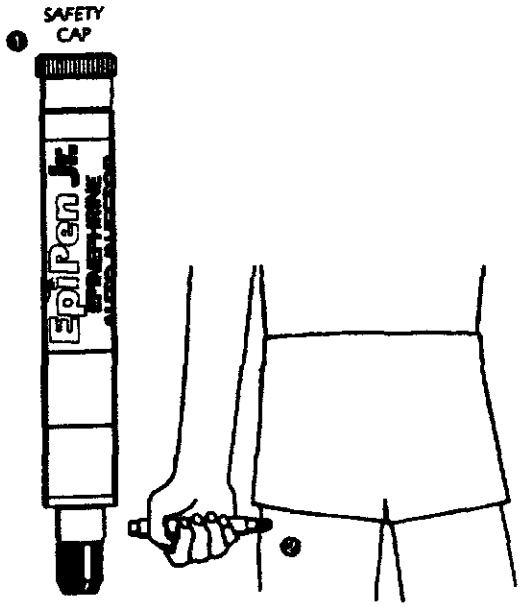
If you have been stung by an insect and experience the signs and symptoms described by your physician, use the EpiPen Jr. Auto-Injector immediately. If possible, remove the insect's stinger with your fingernails; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen Jr., be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN JR. AUTO-INJECTOR

Before using, check to make sure solution in Auto-Injector is not brown in color. (Replace if discolored). Then follow these directions:

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Apply to thigh regardless of what part of the body has been stung.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



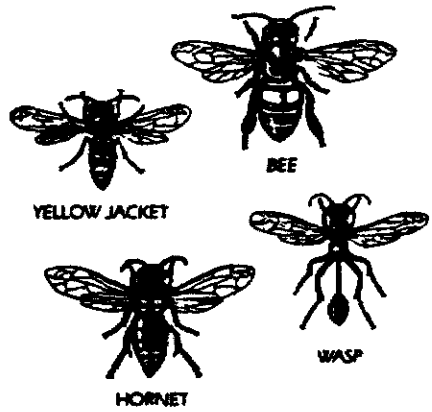
ADDITIONAL PATIENT INFORMATION

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



CONFIDENTIAL

Tear off here and mail to address shown at bottom

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers a free EpiPen® Auto-Injector Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories,
EpiPen Alert,
35 Channel Drive,
Port Washington, N.Y. 11050
U.S.A.

Expiration date. Lot No..

NAME OF PURCHASER _____ (Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

6.

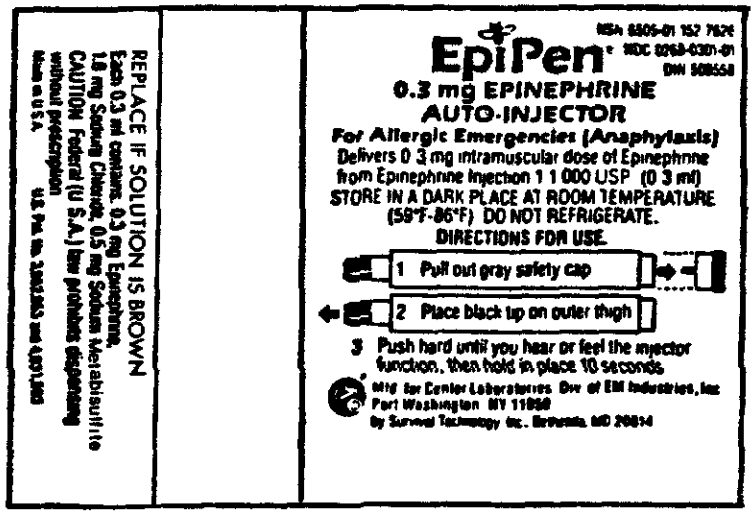
MERIDIAN
01797

CONFIDENTIAL

5. EPIPEN LABEL

CONFIDENTIAL

EPIPEN AUTO-INJECTOR LABEL



Clear Window Area

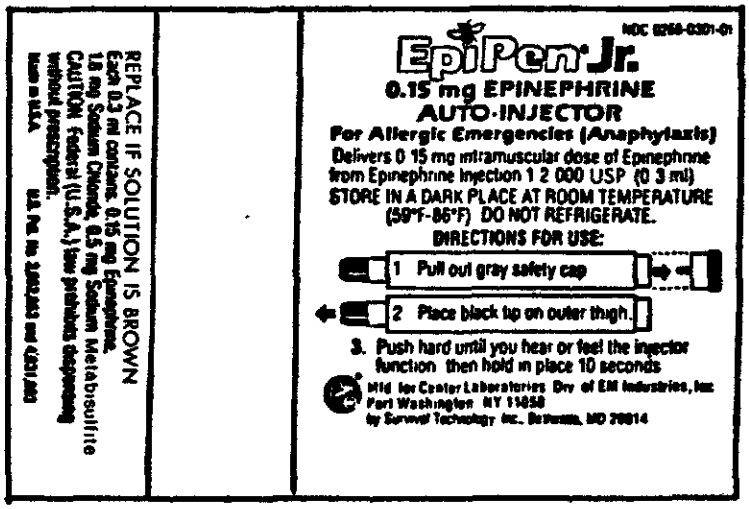
NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

CONFIDENTIAL

6. EPIPEN JR. LABEL

CONFIDENTIAL

EPIPEN JR. AUTO-INJECTOR LABEL



Clear Window Area

NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

NDA 19-430

August 27, 1985

CONFIDENTIAL

MEDICAL OFFICER'S REVIEW

PRODUCT: Epipen and Epipen Jr. Auto-Injectors (epinephrine injection)
ROUTE OF ADMINISTRATION: Intramuscular
CATEGORY OF DRUG: Adrenergic agonist catecholamine
SPONSOR: Survival Technology Inc.
PREVIOUS MEDICAL REVIEWS: See Medical Officer's Review of February 18, 1985.
MATERIAL REVIEWED: Submission of August 26, 1985.

I. This submission contains revised labeling for both Epipen and Epipen Jr.

A. The sponsor has submitted responses made to our labeling recommendations made in the letter to the sponsor of July 23, 1985.

1. Directions for Use: We agree with the sponsor that the sequence of steps should remain the same, as discussed in the meeting of July 5, 1985, with the sponsor.

2. Contraindications Section: The sponsor has made the change requested by us and it is now acceptable.

3. Warnings Section: The sponsor has made the changes requested by us in regard to discoloration of the solution.

4. Warnings Section: The sponsor has capitalized the key warnings as requested by us.

5. Warnings and Precautions Sections: The sponsor has responded to our concerns by dividing the package insert into two parts; one for the patient and one for the physician. This is acceptable, but we have further comments about these sections as noted below.

6. Dosage and Administration Section: We have recommended changes in the wording as noted below.

7. How Supplied Section: The sponsor has made the change requested by us and this is now acceptable.

II. Physician Labeling for Epipen and Epipen Jr. ("Epipen and Epipen Jr. Prescribing Information"). This labeling is acceptable except for the following recommended changes:

A. The last paragraph under Warnings should be the first paragraph under Precautions, and should be changed as follows:

1. "Should be" in the first sentence should be changed to "is ordinarily."

2. "Degenerative" in the first sentence should be deleted.

3. "Ordinarily" should preceed "not recommended" in the second sentence.

4. The last sentence should be removed.

B. Under Precautions in the first sentence of the second paragraph, "administer with caution to" should be removed, and following "body weight" should be the phrase "may be at greater risk of developing adverse reactions after epinephrine administration." The last sentence of the second paragraph should be deleted. The third paragraph should be deleted and replaced with the following paragraph:

> "Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used."

C. Under Adverse Reactions:

1. "Transient and minor" in the beginning of the first sentence of the first paragraph should be removed.

2. "Cardiac" should replace "ventricular" at the beginning of the only sentence in the second paragraph.

D. Under Dosage and Administration:

1. In the first sentence of the second paragraph, "Recommendations regarding" should preceed "dosage," and "when possible" should follow "body weight." The remainder of the first sentence beginning with "in addition to" should be deleted.

2. In the only sentence of the third paragraph, "periodically" should follow "should be" and "by the patient" should follow "visually," and "and should be replaced if these are present" should follow "discoloration" and the rest of the sentence beginning with "prior to" and extending distally should be excised.

E. In the Dosage and Administration section for Epipen Jr., the phrase "and 0.3 mg in adults" should be placed at the end of the second sentence of the second paragraph.

III. Instructions for the Patient:

Under Directions for Using; the first 2 sentences down to "these directions" should be removed,

CONFIDENTIAL

IV. On the Epipen and Epipen Jr. Label, the word "discolored" should replace "brown" on the side panel.

V. In summary if the sponsor makes the changes requested above, this NDA is approvable.

VI. Proposed Draft of Medical Portion of Letter to Sponsor.

(CSO should incorporate the recommendations made above into a letter to the sponsor).

F. Nicklas MD
R. Nicklas, M.D.
8/29/85

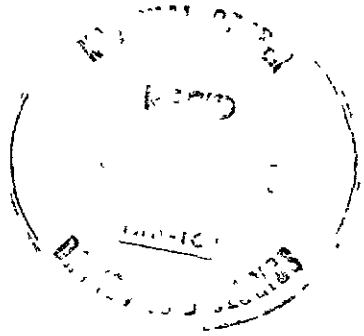
NDA 19-430
HFN-160
HFN-340
DocRm. 160
R.D. RNicklas 8/27/85
R.D. init by:JWWinkler 8/28/85:PHRussell 8/28/85
shg W2055K 8/29/85

Survival Technology, Inc.

CONFIDENTIAL

September 16, 1985

NDA 19-430
Patricia H. Russell, M.D.
Acting Director
Division of Surgical Dental Drug Products
Room 18B-08 HFN 160
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Russell:

Please refer to our new drug application for the EpiPen and EpiPen Jr. Auto-Injector (epinephrine injection, NDA 19-430), our revised labeling submission dated August 26, 1985, and to the Medical Officers Review of the revised labeling dated August 27, 1985.

We appreciate the recommendations made by Dr. Nicklas concerning the Prescribing Information and Patient Instructions as they improve and clarify the information presented to physicians and patients. We have made all of the changes recommended by Dr. Nicklas in his August 27 review with one exception.

Under Precautions, Dr. Nicklas recommended that we delete the third paragraph and replace it with a new papragraph. The paragraph he wished to delete reads as follows: "Use of this product may be inadvisable for patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its components." We feel strongly that the above statement reflects prudent advice concerning the use of this product in patients who have previously reacted abnormally on injection of epinephrine or sulfites. The statement was purposefully placed in the Precautions section as a cautionary statement. It was not placed in the Contraindications section, where such statements normally appear for many other drugs, because of the potential life-saving role of the product.

However, we have modified the statement and incorporated it as the last sentence in the paragraph under Precautions which

MERIDIAN
01805

8101 GLENBROOK ROAD • BETHESDA, MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892684 • CABLE SURTECH, BHDA

CONFIDENTIAL

describes individuals who may be at increased risk of developing adverse reactions after epinephrine administration. The modified statement reads as follows: "Caution should be observed when using this product in patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its ingredients." We have also added the new paragraph suggested by Dr. Nicklas which emphasizes the essential use of epinephrine for the treatment of anaphylaxis.

Copies of the revised labels and labeling are attached for your review and approval. Please feel free to call me at (301) 656-5600 if you have any questions or wish to discuss the revised labeling.

Sincerely,

Gary W. Leyland

Gary W. Leyland
Manager
Clinical and Regulatory Affairs

GW/dl

Attachments

1. EPIPEN PRESCRIBING INFORMATION

EPIPEN 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

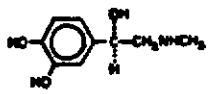
Delivers 0.3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:1,000 (0.3 ml).

DESCRIPTION

The EpiPen Auto-Injector provides epinephrine for emergency intramuscular injection. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 ml) in a sterile solution. Each 0.3 ml contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection.

Epinephrine is a sympathomimetic catecholamine.

Chemically, epinephrine is β-(3,4-dihydroxyphenyl) -α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to hymenoptera stings, foods, drugs and other allergens. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, thereby relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to hymenoptera stings, foods, drugs and other allergens. The EpiPen Auto-Injector is intended for immediate self-administration by individuals with a history of anaphylactic reactions. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59 F-86 F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selec-

tion of an injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

PRECAUTIONS

Epinephrine is ordinarily administered with extreme caution to patients who have developed heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is ordinarily not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium l-thyroxine.

Hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30kg (66lbs.) body weight may be at greater

risk of developing adverse reactions after epinephrine administration. Caution should be observed when using this product in patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its ingredients.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

ADVERSE REACTIONS

Side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessnes, tenseness, anxiety, and fear.

Cardiac arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician should review with the patient, in detail, the patient

instructions and operation of the EpiPen Auto-Injector. Inject the delivered dose of the EpiPen Auto-Injector (0.3 ml Epinephrine Injection, USP, 1:1,000) intramuscularly into the anterolateral aspect of the thigh. See detailed Directions for Use on the accompanying Patient Instructions.

Recommendations regarding dosage in any specific patient should be based on body weight when possible. Usual epinephrine adult dose for allergic emergencies is 0.3 mg. Usual pediatric dose is 0.01 mg/kg body weight. Dosage may be individualized by use of EpiPen and EpiPen Jr. in combination.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection, USP, 1:1,000, 0.3 ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0301-01. Store in a dark place at room temperature (59 F-86 F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue September 1985

Manufactured for Center Laboratories, Division of EM Industries, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

2. EPIPEN JR. PRESCRIBING INFORMATION

EPIPEN Jr. 0.15 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine

For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

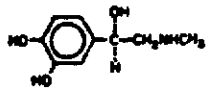
Delivers 0.15 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:2,000 (0.3 ml).

DESCRIPTION

The EpiPen Jr. Auto-Injector provides epinephrine for emergency intramuscular injection. Each EpiPen delivers a single dose of 0.15 mg epinephrine from Epinephrine Injection, USP, 1:2,000 (0.3 ml) in a sterile solution. Each 0.3 ml contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection.

Epinephrine is a sympathomimetic catecholamine.

Chemically, epinephrine is β-(3,4-dihydroxyphenyl) -α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to hymenoptera stings, foods, drugs and other allergens. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, thereby relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to hymenoptera stings, foods, drugs and other allergens. The EpiPen Auto-Injector is intended for immediate self-administration by individuals with a history of anaphylactic reactions. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59 F-86 F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selec-

tion of an injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

PRECAUTIONS

Epinephrine is ordinarily administered with extreme caution to patients who have developed heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is ordinarily not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium l-thyroxine.

Hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30kg (66lbs.) body weight may be at greater

risk of developing adverse reactions after epinephrine administration. Caution should be observed when using this product in patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its ingredients.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

ADVERSE REACTIONS

Side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessnes, tenseness, anxiety, and fear.

Cardiac arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr. should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician

should review with the patient, in detail, the patient instructions and operation of the EpiPen Jr. Auto-Injector. Inject the delivered dose of the EpiPen Jr. Auto-Injector (0.3 ml Epinephrine Injection, USP, 1:2,000) intramuscularly into the anterolateral aspect of the thigh. See detailed Directions for Use on the accompanying Patient Instructions.

Recommendations regarding dosage in any specific patient should be based on body weight when possible. Usual epinephrine dose for allergic emergencies is 0.01mg/kg body weight in pediatric patients and 0.3mg in adults.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Jr. Auto-Injectors (Epinephrine Injection, USP, 1:2,000, 0.3 ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0302-01. Store in a dark place at room temperature (59 F-86 F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue September 1985

Manufactured for Center Laboratories, Division of EM Industries, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

3. EPIPEN PATIENT INSTRUCTIONS

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,
BEFORE AN EMERGENCY ARISES

LOT NO.

CONFIDENTIAL

NDC 0268-0301-01

DIN 509558 EPIPEN

NSN 6305-01-152-7626

EPINEPHRINE AUTO-INJECTOR
FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.3 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:1,000(0.3 ml)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (59 F-86 F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Industries, Inc., Port Washington, NY 11050, U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814 U.S.A.

MERIDIAN
01824

/.

US Patent No 3,882,863 and 4,031,893

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Auto-Injector should be used only by hypersensitive (allergic) individuals in the event of an allergic emergency as prescribed by a physician.

THE EPIPEN AUTO-INJECTOR

The EpiPen Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.3 mg of epinephrine.

*Keep the EpiPen Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Auto Injector is designed with a see through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

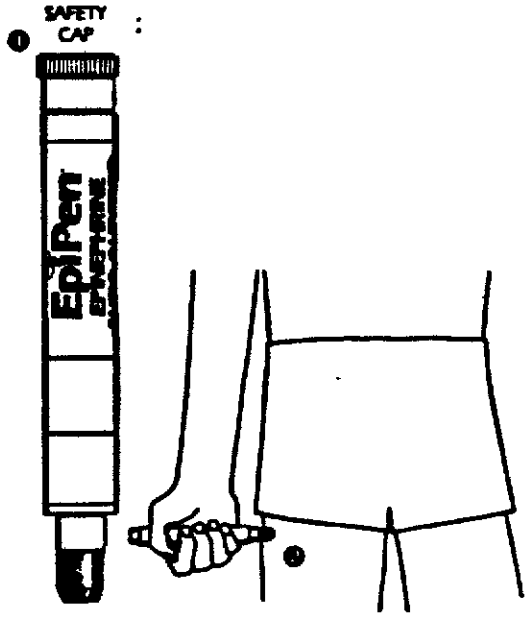
EMERGENCY TREATMENT OF INSECT STING ALLERGY

If you have been stung by an insect and experience the signs and symptoms described by your physician, use the EpiPen Auto-Injector immediately. If possible, remove the insect's stinger with your fingernails; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen , be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Apply to thigh regardless of what part of the body has been stung.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



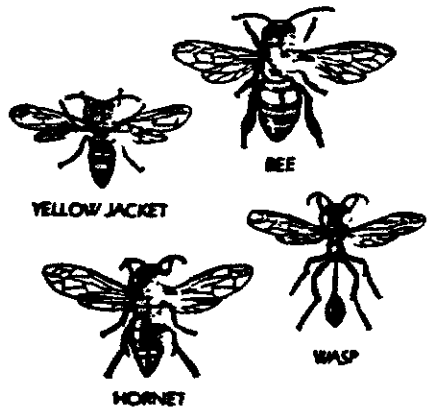
ADDITIONAL PATIENT INFORMATION

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



CONFIDENTIAL

Tear off here and mail to address shown at bottom

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers a free EpiPen® Auto-Injector Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories,
EpiPen Alert,
35 Channel Drive,
Port Washington, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____ (Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

MERIDIAN
01829

6.

4. EPIPEN JR. PATIENT INSTRUCTIONS

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,
BEFORE AN EMERGENCY ARISES

LOT NO.

CONFIDENTIAL

NDC 0268-0302-01

DIN 509558

EPIPEN JR.

EPINEPHRINE AUTO-INJECTOR
FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:2,000(0.3 ml)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (59 F-86 F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Industries, Inc., Port Washington, NY 11050, U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814 U.S.A.

MERIDIAN
01831

US Patent No 3,882,863 and 4,031,893

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Jr. Auto-Injector should be used only by hypersensitive (allergic) individuals in the event of an allergic emergency as prescribed by a physician.

THE EPIPEN JR. AUTO-INJECTOR

The EpiPen Jr. Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.15 mg of epinephrine.

*Keep the EpiPen Jr. Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Jr. Auto Injector is designed with a see through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

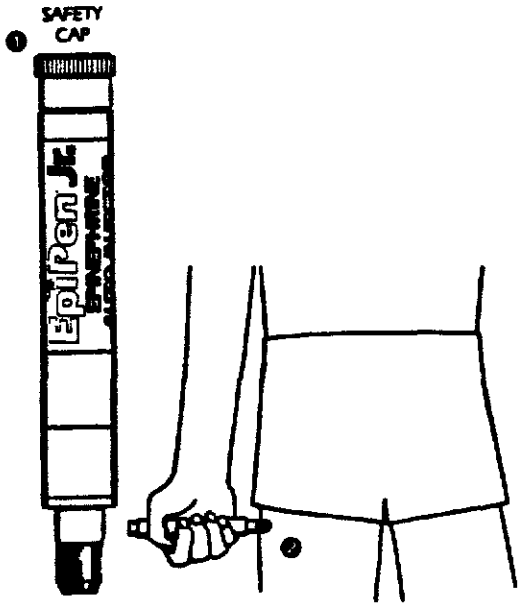
EMERGENCY TREATMENT OF INSECT STING ALLERGY

If you have been stung by an insect and experience the signs and symptoms described by your physician, use the EpiPen Jr. Auto-Injector immediately. If possible, remove the insect's stinger with your fingernails; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen Jr., be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN JR. AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Apply to thigh regardless of what part of the body has been stung.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



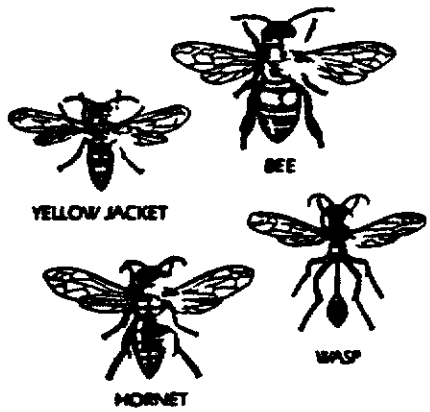
ADDITIONAL PATIENT INFORMATION

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



CONFIDENTIAL

Tear off here and mail to address shown at bottom

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers a free EpiPen® Auto-Injector Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories,
EpiPen Alert,
35 Channel Drive,
Port Washington, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____ (Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

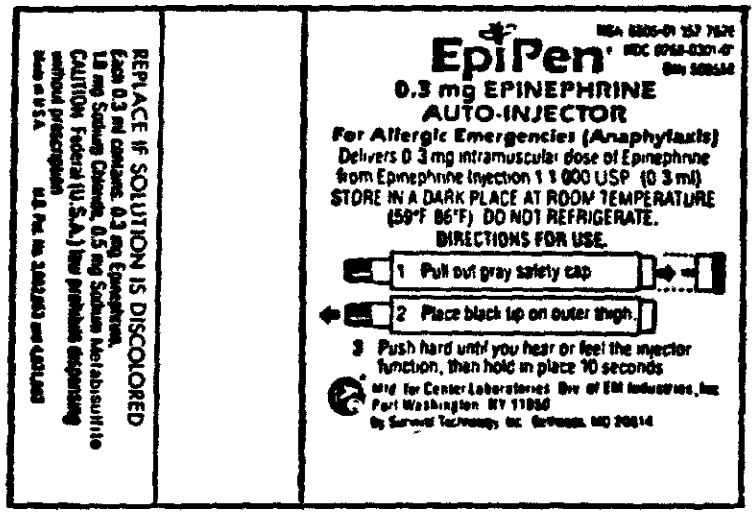
MERIDIAN
01836

6.

5. EPIPEN LABEL

CONFIDENTIAL

EPIPEN AUTO-INJECTOR LABEL



Clear Window Area

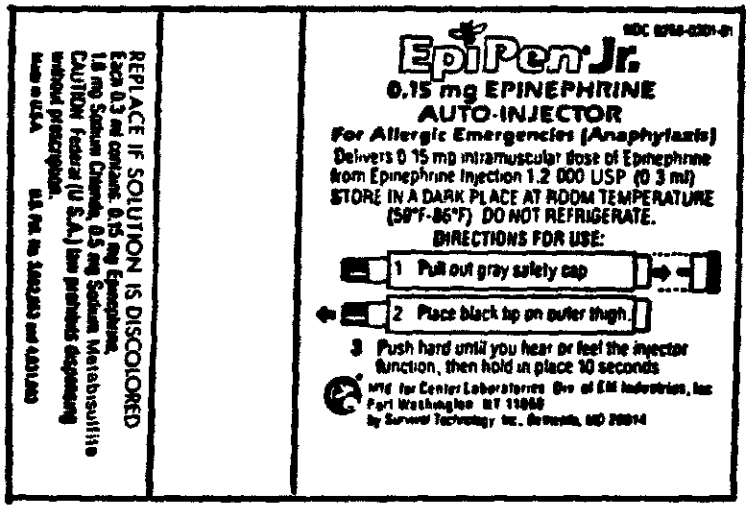
NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

CONFIDENTIAL

6. EPIPEN JR. LABEL

CONFIDENTIAL

EPIPEN JR. AUTO-INJECTOR LABEL



Clear Window Area

NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

Survival Technology, Inc.

January 27, 1987

NDA 19-430

Patricia H. Russell, M.D.
Director
Division of Surgical-Dental Drug Products
Room 18B-08 HFN 160
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Russell:

Please refer to our new drug application for EpiPen and EpiPen Jr. Auto-Injectors (epinephrine injection) NDA 19-430. Also, refer to the draft labeling submitted to you on September 16, 1985 and reviewed by Dr. Richard Niklas on September 17, 1985. This labeling was deemed approvable by Dr. Niklas.

We are submitting a labeling amendment to include the addition of the pH range in the DESCRIPTION section, the addition of a sulfite warning statement in the WARNINGS section, and deletion of a statement in the precautions section which is redundant. In addition, we have included copies of the patient instructions and immediate container labels for reference. There are no changes in these items.

We appreciate your prompt review of this material. Please call me at (301) 656-5600 if you have any questions.

Sincerely,

Gary W. Leyland
Manager
Clinical and Regulatory Affairs

Enclosures

MERIDIAN
01499

8101 GLENBROOK ROAD • BETHESDA, MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892694 • CABLE SURTECH, BHDA

1. EPIPEN PRESCRIBING INFORMATION

EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

Delivers 0.3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:1,000 (0.3 ml).

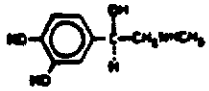
DESCRIPTION

The EpiPen Auto-Injector provides epinephrine for emergency intramuscular injection. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 ml) in a sterile solution. Each 0.3 ml contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. ← INSERT The pH range is 2.5-5.0.

Epinephrine is a sympathomimetic catecholamine.

MERIDIAN 01501

Chemically, epinephrine is β-(3,4-dihydroxyphenyl) -α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to hymenoptera stings, foods, drugs and other allergens. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, thereby relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to hymenoptera stings, foods, drugs and other allergens. The EpiPen Auto-Injector is intended for immediate self-administration by individuals with a history of anaphylactic reactions. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59 F-86 F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selec-

tion of an injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

INSERT →

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

PRECAUTIONS

Epinephrine is ordinarily administered with extreme caution to patients who have developed heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is ordinarily not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium l-thyroxine.

Hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30kg (66lbs.) body weight may be at greater

risk of developing adverse reactions after epinephrine administration. ~~Caution should be observed when using this product in patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its ingredients.~~ DELETE

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

ADVERSE REACTIONS

Side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessnes, tenseness, anxiety, and fear.

Cardiac arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician should review with the patient, in detail, the patient

instructions and operation of the EpiPen Auto-Injector. Inject the delivered dose of the EpiPen Auto-Injector (0.3 ml Epinephrine Injection, USP, 1:1,000) intramuscularly into the anterolateral aspect of the thigh. See detailed Directions for Use on the accompanying Patient Instructions.

Recommendations regarding dosage in any specific patient should be based on body weight when possible. Usual epinephrine adult dose for allergic emergencies is 0.3 mg. Usual pediatric dose is 0.01 mg/kg body weight. Dosage may be individualized by use of EpiPen and EpiPen Jr. in combination.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection, USP, 1:1,000, 0.3 ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0301-01. Store in a dark place at room temperature (59° F-86° F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue January 1987

Manufactured for Center Laboratories, Division of EM Industries, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

MERIDIAN 01507

7.

2. EPIPEN JR. PRESCRIBING INFORMATION

CONFIDENTIAL

EPIPEN® Jr. 0.15 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

Delivers 0.15 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:2,000 (0.3 ml).

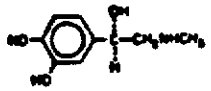
DESCRIPTION

The EpiPen Jr. Auto-Injector provides epinephrine for emergency intramuscular injection. Each EpiPen delivers a single dose of 0.15 mg epinephrine from Epinephrine Injection, USP, 1:2,000 (0.3 ml) in a sterile solution. Each 0.3 ml contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. ← INSERT The pH range is 2.5-5.0.

Epinephrine is a sympathomimetic catecholamine.

MERIDIAN 01509

Chemically, epinephrine is β-(3,4-dihydroxyphenyl) -α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to hymenoptera stings, foods, drugs and other allergens. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, thereby relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to hymenoptera stings, foods, drugs and other allergens. The EpiPen Auto-Injector is intended for immediate self-administration by individuals with a history of anaphylactic reactions. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59 F-86 F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selec-

risk of developing adverse reactions after epinephrine administration. ~~Caution should be observed when using this product in patients who have previously demonstrated an acute hypersensitivity reaction on injection of any of its ingredients.~~ DELETE

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

ADVERSE REACTIONS

Side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessnes, tenseness, anxiety, and fear.

Cardiac arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr. should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician

should review with the patient, in detail, the patient instructions and operation of the EpiPen Jr. Auto-Injector. Inject the delivered dose of the EpiPen Jr. Auto-Injector (0.3 ml Epinephrine Injection, USP, 1:2,000) intramuscularly into the anterolateral aspect of the thigh. See detailed Directions for Use on the accompanying Patient Instructions.

Recommendations regarding dosage in any specific patient should be based on body weight when possible. Usual epinephrine dose for allergic emergencies is 0.01mg/kg body weight in pediatric patients and 0.3mg in adults.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Jr. Auto-Injectors (Epinephrine Injection, USP, 1:2,000, 0.3 ml) are available singly or in packages of six (pharmacy pack), NDC 0268-0302-01. Store in a dark place at room temperature (59 F-86 F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue January 1987

Manufactured for Center Laboratories, Division of EM Industries, Inc. 35 Channel Drive, Port Washington, NY 11050, U.S.A. by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

3. EPIPEN PATIENT INSTRUCTIONS

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,

BEFORE AN EMERGENCY ARISES

LOT NO.

NDC 0268-0301-01

DIN 509558

EPIPEN®

NSN 6305-01-152-7626

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.3 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:1,000(0.3 ml)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (59 F-86 F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Industries, Inc., Port Washington, NY 11050, U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814 U.S.A.

MERIDIAN 01517

US Patent No 3,882,863 and 4,031,893

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Auto-Injector should be used only by hypersensitive (allergic) individuals in the event of an allergic emergency as prescribed by a physician.

THE EPIPEN AUTO-INJECTOR

The EpiPen Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.3 mg of epinephrine.

*Keep the EpiPen Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Auto Injector is designed with a see through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF INSECT STING ALLERGY

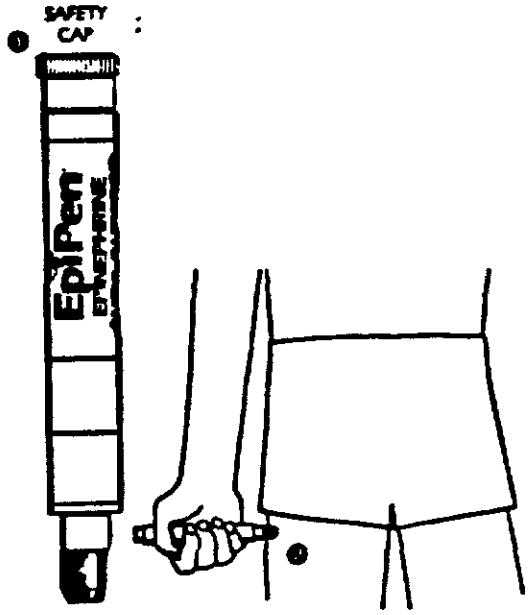
If you have been stung by an insect and experience the signs and symptoms described by your physician, use the EpiPen Auto-Injector immediately. If possible, remove the insect's stinger with your fingernails; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen , be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

3.

DIRECTIONS FOR USING EPIPEN® AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Apply to thigh regardless of what part of the body has been stung.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



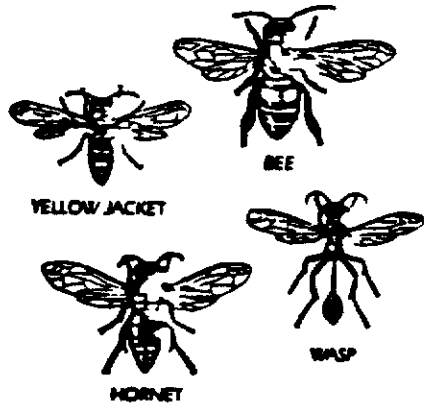
ADDITIONAL PATIENT INFORMATION

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



Tear off here and mail to address shown at bottom

EPIPEN AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers a free EpiPen® Auto-Injector Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories,
EpiPen Alert,
35 Channel Drive,
Port Washington, N.Y. 11050
U.S.A.

Expiration date _____ *Lot No* _____

NAME OF PURCHASER _____ (Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

6.

MERIDIAN
01522

4. EPIPEN JR. PATIENT INSTRUCTIONS

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,

BEFORE AN EMERGENCY ARISES

LOT NO.

NDC 0268-0302-01

DIN 509558

EPIPEN® JR.

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:2,000(0.3 ml)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (59 F-86 F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Industries, Inc., Port Washington, NY 11050, U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814 U.S.A.

MERIDIAN 01524

US Patent No 3,882,863 and 4,031,893

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Jr. Auto-Injector should be used only by hypersensitive (allergic) individuals in the event of an allergic emergency as prescribed by a physician.

THE EPIPEN JR. AUTO-INJECTOR

The EpiPen Jr. Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.15 mg of epinephrine.

*Keep the EpiPen Jr. Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Jr. Auto Injector is designed with a see through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

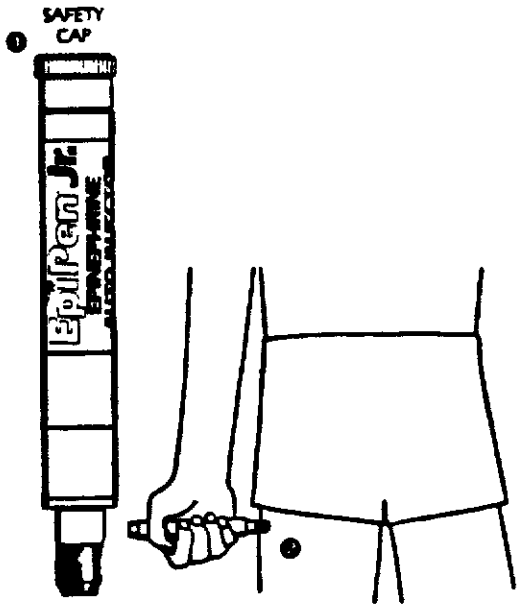
EMERGENCY TREATMENT OF INSECT STING ALLERGY

If you have been stung by an insect and experience the signs and symptoms described by your physician, use the EpiPen *Jr.* Auto-Injector immediately. If possible, remove the insect's stinger with your fingernails; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen Jr., be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN JR. AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Apply to thigh regardless of what part of the body has been stung.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



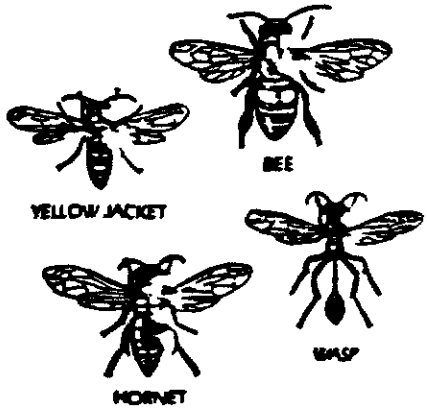
ADDITIONAL PATIENT INFORMATION

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



5.

Tear off here and mail to address shown at bottom

EPIPEN AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers a free EpiPen® Auto-Injector Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories,
EpiPen Alert,
35 Channel Drive,
Port Washington, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____
(Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

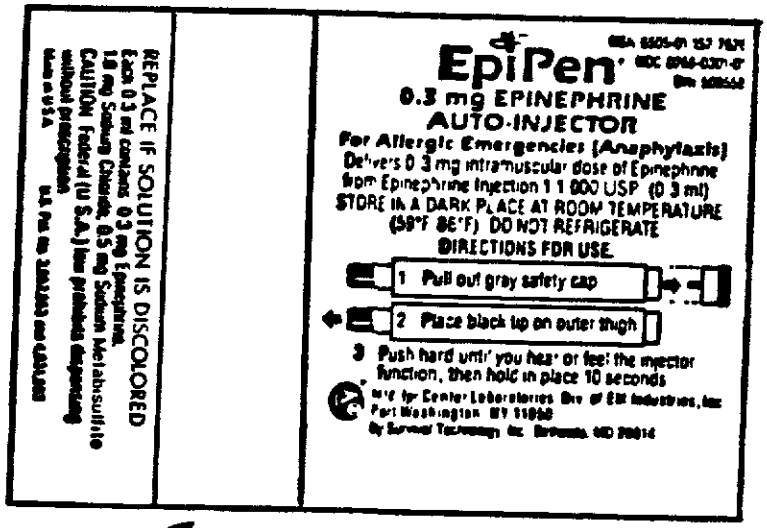
CITY _____ STATE _____ ZIP _____

6.

MERIDIAN
01529

5. EPIPEN LABEL

EPIPEN AUTO-INJECTOR LABEL

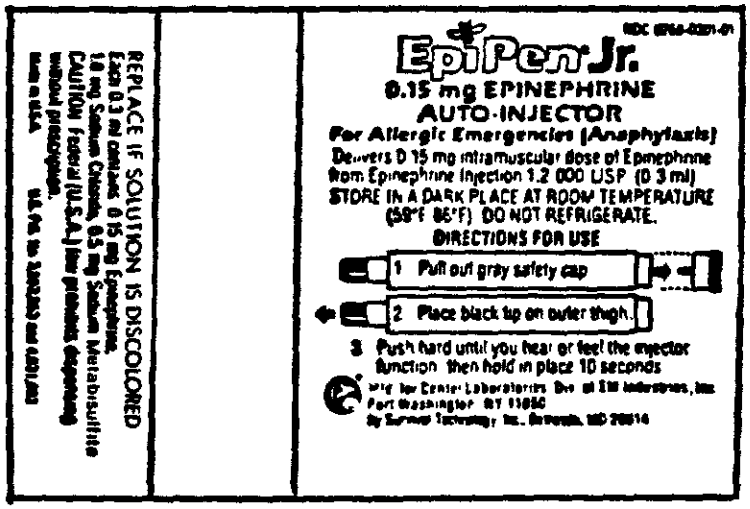


Clear Window Area

NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

6. EPIPEN JR. LABEL

EPIPEN JR. AUTO-INJECTOR LABEL



Clear Window Area

NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430

OCT 23 1987

OCT 2 7 1987

Survival Technology, Inc.
8101 Glenbrook Road
Bethesda, MD 20814

Attention: Gary W. Leyland
Manager
Clinical and Regulatory Affairs

Gentlemen:

Please refer to your new drug application dated January 31, 1985, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for EpiPen and EpiPen Jr. Auto-Injectors (epinephrine injection).

We also acknowledge receipt of your additional communications dated April 29, June 18, July 3, July 5, August 26, September 16, October 11 and November 7, 1985, May 19, July 24 and December 16, 1986, and January 27, 1987, amending the application.

We have completed our review of this application and it is approvable. Before the application may be approved, however, we request that you submit the following:

I. Please provide the patent information as required by section 505(b)(1) of the Act.

II. Please provide the safety update report in accordance with 314.50(d)(5)(vi)(b).

III. Please submit draft labeling that is identical to the draft copy submitted on January 27, 1987, except for the following changes:

EpiPen Package Insert

A. Clinical Pharmacology:

1. Change "hymenoptera" in the 2nd sentence to "insect".

2. Add "or bites" after "stings" in the second sentence.

3. Remove the word "resulting" from the third sentence.

4. Replace "capillary" with "vascular" in the third sentence.

CONFIDENTIAL

5. Add "which can lead to loss of intravascular volume and hypotension during anaphylactic reactions" at the end of the third sentence.

6. The fourth sentence should be changed to read "Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which will alleviate wheezing and dyspnea."

7. The last sentence should be changed to read, "Epinephrine also alleviates pruritis, urticaria, and angioedema, and may be effective in relieving gastrointestinal or genitourinary symptoms associated with anaphylaxis."

8. An additional sentence should be added between what is now the second and third sentence which states that "Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action."

9. An addition to the old third sentence should read "through its effect on alpha adrenergic receptors" and follow "The strong vasoconstrictor action of epinephrine."

10. An additional sentence should be added after the second sentence and read, "It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis."

11. This section will now read:

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth muscle

causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

B. Indications and Usage:

1. The first sentence should be changed to read, "Epinephrine.....to insect stings or bites, foods....". The proposed changes are underlined.

2. The phrase "as well as idiopathic or exercise-induced anaphylaxis", should follow "and other allergen" at the end of the first sentence.

3. The second sentence should be changed to read, "The EpiPen .....by a person with a history of an anaphylactic reaction." The proposed changes are underlined.

4. The statement that, "Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema." should be added as an additional sentence after the second sentence.

5. The third sentence in the original labeling, which is now the fourth and last sentence, should begin with "The EpiPen" rather than "It".

6. The word "immediate" should replace "subsequent" in the last sentence.

C. Warnings:

1. Remove "Every effort should be made to" from the beginning of the sixth sentence. The sixth sentence will now read "Avoid possible inadvertent intravascular administration."

2. There will now be a new sentence between the present sixth and seventh sentence, which will read, "Select an appropriate injection site such as the thigh."

D. Precautions:

1. The following paragraph should be the first paragraph in this section:

"Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insert stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration.(see Dosage and Administration)

2. The paragraph which is currently the first paragraph in this section will now be the second paragraph.

3. Remove the word "developed" from the first sentence of the new second paragraph.

4. After the word "arrhythmias" in the second sentence of the new second paragraph should be examples supplied by you.

5. The single sentence in the old second paragraph which is now the third paragraph should be changed as follows:

   a. The phrase "and sodium L-thyroxine" should be deleted.

   b. You should clarify the basis for the statement that antihistamines potentiate the effects of epinephrine.

6. In regard to the old third paragraph which is now the fourth paragraph:

   a. "psychoneurotic individuals" should be removed.

   b. You should provide data to substantiate the statement that "elderly individuals, pregnant woman, and children under 30 kg (66 lbs.) body weight may be at greater risk of developing adverse reactions after epinephrine administration."

7. Include monamine oxidase inhibitors among the drugs listed in the second paragraph.

E. Carcinogenicity, Mutagenicity, and Impairment of Fertility:

There is currently no such section in the labeling. You should draft appropriate comments for this section of the labeling.

F. Usage in Pregnancy:

There is currently no section of this type in the labeling. Based on the data available, you should propose appropriate labeling for this section. It should be made clear, however, that risks in pregnancy from epinephrine are secondary to risks from anaphylaxis when this section is added.

G. Pediatric Use:

Please add this section to the labeling and refer to EpiPen Jr. labeling as well.

H. Adverse Reactions:

The first paragraph in this section should read, "Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety." The additional adverse effects are underlined. The words "throbbing", "tenseness", and "fear" should be removed.

I. Dosage and Administration:

1. The second sentence of the first paragraph should be changed to read, "The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr. to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen Auto Injector."

2. The first sentence of the second paragraph should be removed.

3. The third sentence of the second paragraph should be deleted and replaced with the following sentence, "For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient (see labeling for EpiPen Jr.)."

4. A new fourth sentence of the second paragraph should read, "However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed."

5. The following sentence should follow the new fourth sentence of the second paragraph; "The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children."

6. As a new third paragraph should be the following sentence, "With severe persistent anaphylaxis, repeat injections with an additional EpiPen may be necessary."

J. Overdosage:

There is currently no overdosage section. You should add this section to the labeling.

K. How Supplied:

The storage statements in the package insert and on all labels should be stated in Celsius (C^0) followed by Fahrenheit (F^0).

EpiPen and EpiPen Jr. Patient Instructions:

A. The second sentence of the initial paragraph should be changed to read, "The EpiPen Auto-Injector should be used only by a hypersensitive (allergic) person in an allergic emergency as prescribed by a physician."

B. An additional third sentence should read, "Such emergencies may occur from insect stings or bites, foods, drugs or other allergens, as well as idiopathic or exercise-induced anaphylaxis."

For package inserts and patient instructions, clarify whether injections through clothing are recommended.

Should additional information relating to the safety or effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit, in duplicate, advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Surgical-Dental Drug Products (HFN-160), and the second copy to the Division of Drug Advertising and Labeling (HFN-240), Room 10B-04, 5600 Fishers Lane, Rockville, MD 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use FD-2253 for this submission; this form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

Sincerely yours,

Paula Botstein MD

Paula Botstein, M.D.
Deputy Director (Medical Affairs)
Office of Drug Research and Review
Center for Drug Evaluation and Research

Survival Technology, Inc.

November 2, 1987

NDA 19-430
Philip G. Walters, M.D.
Director
Division of Surgical-Dental Drug Products
HFN 160 Room 18B08
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Walters:

Please refer to our new drug application for EpiPen and EpiPen Jr. Auto-Injectors (epinephrine injection), and to the approvable letter dated October 23, 1987, for this NDA.

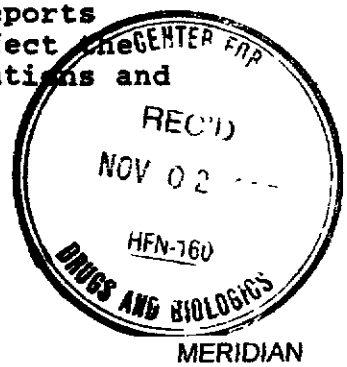
We are amending the application to provide the following information as requested in the approvable letter:

I. Patent information per section 505(b)(1) of the Act.

We certify that Patent No. 3,712,301, expiring on January 23, 1990, Patent No. 3,797,489, expiring on March 19, 1991, Patent No. 3,882,863, expiring on March 19, 1991, and Patent No. 4,031,893, expiring on June 28, 1994, each of which is a valid patent, cover the EpiPen and EpiPen Jr. Auto-Injector drug products (i.e., epinephrine injectable in a prefilled disposable spring-loaded automatic hypodermic injection device).

II. Safety update report in accordance with 314.50 (d)(5)(vi)(b).

We have performed searches of the scientific literature via MEDLINE and TOXLINE for new information regarding the safety of epinephrine. The searches covered the period from January, 1985, to the present. There were no reports containing new safety information that would affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.



8101 GLENBROOK ROAD • BETHESDA, MARYLAND 20814 • TELEPHONE (301) 656-
TELEX 892694 • CABLE SURTECH, BHDA

MERIDIAN
01552

III. Draft Labeling

See enclosures 1 through 5 for labeling. We have made all of the changes requested in the approvable letter. Text is provided for the following sections: Carcinogencity, Mutagenicity, and Impairment of Fertility; Usage in Pregnancy, and Pediatric Use.

We have made the following additional changes in the package inserts and patient instructions:

EpiPen and EpiPen Jr. Package Inserts

A. Description:

1. Changed first sentence from "The EpiPen Auto-Injector provides epinephrine for emergency intramuscular injection," to "The EpiPen Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use." This change is needed to inform the prescriber and pharmacist that the injector contains 2 mL of solution even though it dispenses only 0.3 mL.

B. Precautions:

1. The single sentence in the third paragraph has been changed as follows:

   The words "certain antihistamines, e.g., diphenhydramine tripelennamine, d-clorpheniramine" are deleted. The sentence now reads "The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors."

2. The word "theoretically" has been added between the words "be" and "at" in the fourth line in the fourth paragraph.

C. Dosage and Administration:

1. The following words have been added to the third sentence in the first paragraph: "through clothing if necessary."

2. For the EpiPen Jr. insert only, the dosage formula for pediatric patients has been added to the end of the second line in the second paragraph as follows: "(0.01 mg/Kg body weight)".

EpiPen and EpiPen Jr. Patient Instructions

A. On page three, the heading "EMERGENCY TREATMENT OF INSECT STING ALLERGY', has been changed to read "EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS".

B. The first sentence in the first paragraph under the above heading is changed to read, "If you experience the signs and symptoms described by your physician, use the EpiPen Auto-Injector immediately, through clothing if necessary."

The second sentence in the same paragraph is changed to read, "If you have been stung by an insect, remove the insect's stinger with your fingernails, if possible; do not squeeze, pinch or push it deeper into the skin."

C. On page 5, under "DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR", direction number 2, insert "always" before "apply to the thigh". Delete the remainder of the sentence "regardless of what part of the body has been stung."

D. On page 5, the numbers on the drawing have been changed from white on black to black on white. The number 2 has been moved to the left, off of the patient's leg, to avoid confusion as to the correct injection site.

E. On page 6, the heading "ADDITIONAL PATIENT INFORMATION" has been changed to "ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS".

F. On page 7, second sentence in the Auto-Injector Alert paragraph, delete the words "free EpiPen Auto-Injector". Change "a" to "an". The sentence now reads "For your safety and convenience, Center Laboratories offers an Alert Service."

IV. Advertising Copy

See enclosure 6 for advertising copy that is currently in use for EpiPen and EpiPen Jr. Auto-Injectors. The full disclosure section of the ads will be replaced with the text from the revised package inserts when approved.

In addition to the above information, I have enclosed a revised copy of the Sodium Metabisulfite Assay procedure (Enclosure 7). The procedure incorporates the following minor revisions as requested in your letter dated September 2, 1987:

1. A note has been added to the standard preparation instructing that the standard employed match the claimed species.

2. The sample preparation has been changed to provide clear instructions for the pooling of syringe contents or other individual dosage forms.

3. A specification for the determination of a resolution factor (R) has been added to the system suitability requirements.

Please call me at (301) 656-5600 if you need any additional information. We look forward to your prompt review of this amendment.

Sincerely,

Gary W. Leyland
Manager
Clinical and
Regulatory Affairs

DRAFT
11/2/87

1. EPIPEN PRESCRIBING INFORMATION

DRAFT
11/2/87

EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

Delivers 0.3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 mL).

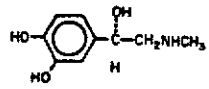
DESCRIPTION

The EpiPen Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 mL) in a sterile solution. Each 0.3 mL contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5-5.0.

Epinephrine is a sympathomimetic catecholamine.

DRAFT
11/2/87

Chemically, epinephrine is β-(3,4-dihydroxyphenyl)-α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic

receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apphrehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal

cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15°-30° C/ 59°-86° F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. Select an appropriate injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT

INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used. It must be

clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration. (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease. Use of epinephrine with drugs that may sensitize the heart to arrhythmias, e.g., digitalis, mercurial diuretics, or quinidine, ordinarily is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30 kg (66 lbs.) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

USAGE IN PREGNANCY

Pregnancy Category C: Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose. There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage

appropriate to body weight (see Dosage and Administration).

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety.

Cardiac arrhythmias may follow administration of epinephrine.

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure. Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac

stimulation. Rapidly acting vasodilators such as nitrites, or alpha-blocking agents may counteract the marked pressor effects.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr. to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen Auto-Injector. Inject the delivered dose of the EpiPen Auto-Injector (0.3 mL Epinephrine Injection, USP, 1:1000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. See detailed Directions for Use on the accompanying Patient Instructions.

Usual epinephrine adult dose for allergic emergencies is

0.3 mg. For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient (see labeling for EpiPen Jr.). However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed. The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children.

With severe persistent anaphylaxis, repeat injections with an additional EpiPen may be necessary.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection, USP, 1:1000, 0.3 mL) are available singly or in packages of six (pharmacy pack), NDC 0268-0301-01. Store in a dark

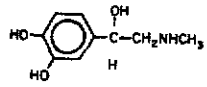
place at room temperature (15°-30°C/59°-86°F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Date of Issue November 1987

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
by Survival Technology, Inc., Bethesda, MD 20814, U.S.A

Chemically, epinephrine is β-(3,4-dihydroxyphenyl)-α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic

DRAFT
11/2/87

2. EPIPEN JR. PRESCRIBING INFORMATION

DRAFT
11/2/87

EPIPEN® JR. 0.15 mg EPINEPHRINE AUTO-INJECTOR
Auto-Injector for Intramuscular Injection
of Epinephrine
For the Emergency Treatment of Allergic
Reactions (Anaphylaxis)

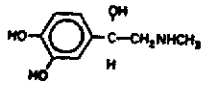
Delivers 0.15 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:2000 (0.3 mL).

DESCRIPTION

The EpiPen Jr. Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Jr. Auto-Injector delivers a single dose of 0.15 mg epinephrine from Epinephrine Injection, USP, 1:2000 (0.3 mL) in a sterile solution. Each 0.3 mL contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5 - 5.0.

Epinephrine is a sympathomimetic catecholamine.

Chemically, epinephrine is β-(3,4-dihydroxyphenyl)-α-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. EpiPen Jr. Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth

muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen Jr. Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apphrehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema.

DRAFT
11/2/87

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15°-30°C/59°-86°F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. Select an appropriate injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated

with epinephrine administration. (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease. Use of epinephrine with drugs that may sensitize the heart to arrhythmias, e.g., digitalis, mercurial diuretics, or quinidine, ordinarily is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 15 kg (33 lbs.) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with

these conditions should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

USAGE IN PREGNANCY

Pregnancy Category C: Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose. There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration).

DRAFT
11/2/87

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety.

Cardiac arrhythmias may follow administration of epinephrine.

OVERDOSAGE

Overdosage or inadvertent ıntravascular ınjection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure. Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Rapidly acting vasodilators such as nitrites, or alpha-blocking agents may counteract the marked pressor effects.

DRAFT
11/2/87

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr. should take appropriate steps to insure that his patient understands the indications and use of this device thoroughly. The physician should review with the patient or any other person who might be in a position to administer EpiPen Jr. to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen Jr. Auto-Injector. Inject the delivered dose of the EpiPen Jr. Auto-Injector (0.3 mL Epinephrine Injection, USP, 1:2000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. See detailed Directions for Use on the accompanying Patient Instructions.

Usual epinephrine adult dose for allergic emergencies is 0.3 mg. For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient (0.01 mg/Kg body weight). However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug

is being prescribed. The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children.

With severe persistent anaphylaxis, repeat injections with an additional EpiPen Jr. may be necessary.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Jr. Auto-Injectors (Epinephrine Injection, USP, 1:2000, 0.3 mL) are available singly or in packages of six (pharmacy pack), NDC 0268-0302-1. Store in a dark place at room temperature (15°-30°C/59°-86°F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

DRAFT
11/2/87

Date of Issue November 1987

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc.

35 Channel Drive, Port Washington, NY 11050, U.S.A.

by Survival Technology, Inc., Bethesda, MD 20814, U.S.A

DRAFT
11/2/87

EPIPEN® JR. 0.15 mg EPINEPHRINE AUTO-INJECTOR
Auto-Injector for Intramuscular Injection of Epinephrine For the Emergency Treatment of Allergic Reactions (Anaphylaxis)

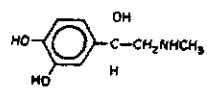
Delivers 0.15 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:2000 (0.3 mL).

DESCRIPTION

The EpiPen Jr. Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Jr. Auto-Injector delivers a single dose of 0.15 mg epinephrine from Epinephrine Injection, USP, 1:2000 (0.3 mL) in a sterile solution. Each 0.3 mL contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5 - 5.0.

Epinephrine is a sympathomimetic catecholamine.

Chemically, epinephrine is β-(3,4-dihydroxyphenyl)-α-methylaminoethanol, with the following structure:



DRAFT

11/2/87

3. EPIPEN PATIENT INSTRUCTIONS

DRAFT
11/2/87

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,

BEFORE AN EMERGENCY ARISES

LOT NO.

NDC 0268-0301-01

DIN 509558

EPIPEN®

NSN 6305-01-152-7626

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.3 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:1,000(0.3mL)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C/59°-86°F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc., Port Washington, NY 11050, U.S.A.

DRAFT
11/2/87

by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

US Patent No. 3,882,863, 4,031,893 and 3,712,301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Auto-Injector should be used only by a hypersensitive (allergic) person in an allergic emergency as prescribed by a physician. Such emergencies may occur from insect stings or bites, foods, drugs or other allergens, as well as idiopathic or exercise-induced anaphylaxis.

THE EPIPEN AUTO-INJECTOR

The EpiPen Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver

a single dose of 0.3 mg of epinephrine.

*Keep the EpiPen Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Auto-Injector is designed with a see-through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

If you experience the signs and symptoms described by your physician, use the EpiPen Auto-Injector immediately, through clothing if necessary. If you have been stung by an insect, remove the insect's stinger with your fingernails if possible; do not squeeze, pinch

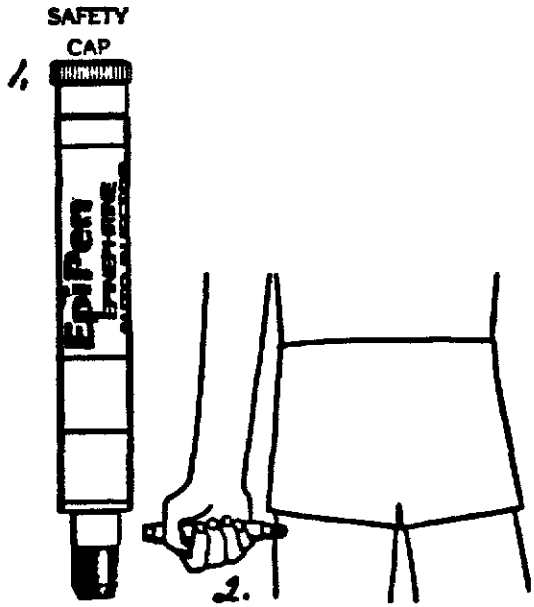
or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen, be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DRAFT
11/2/87

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Always apply to thigh.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



DRAFT
11/2/87

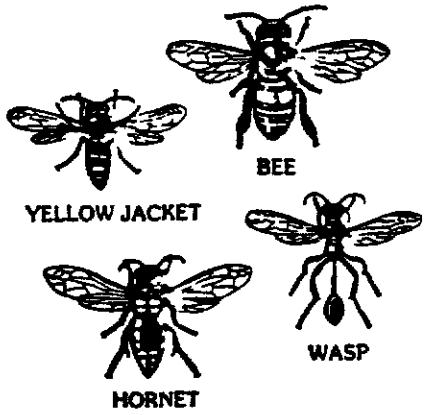
ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



(NOT TO SCALE)

-----Tear off here and mail to address shown at bottom-----

EPIPEN AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:

Center Laboratories
EpiPen Alert
35 Channel Drive
Port Washington, NY 11050
U.S.A.

Expiration Date: Lot No.:

Name of Purchaser:

(Please Print)

Address:

City: State: Zip:

Date of Purchase:

I purchased my EpiPen Auto-Injector at:

Pharmacy Name_____

Address_____

City_____State_____Zip___

MERIDIAN
01589

DRAFT
11/2/87

CONFIDENTIAL

4. EPIPEN JR. PATIENT INSTRUCTIONS

DRAFT
11/2/87

EXP. DATE:

READ INSTRUCTIONS CAREFULLY,

BEFORE AN EMERGENCY ARISES

LOT NO.

CONFIDENTIAL

NDC 0268-0302-01

DIN 509558

EPIPEN® JR.

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION, USP, 1:2,000(0.3 mL)

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C / 59°-86°F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc., Port Washington, NY 11050, U.S.A.

DRAFT
11/2/87

by Survival Technology, Inc., Bethesda, MD 20814, U.S.A.

CONFIDENTIAL

US Patent Nos. 3,882,863, 4,031,893 and 3,712,301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Jr. Auto-Injector should be used only by a hypersensitive (allergic) person in the event of an allergic emergency as prescribed by a physician. Such emergencies may occur from insect stings or bites, foods, drugs or other allergens, as well as idiopathic or exercise-induced anaphylaxis.

THE EPIPEN JR. AUTO-INJECTOR

DRAFT
11/2/87

CONFIDENTIAL

The EpiPen Jr. Auto-Injector is a disposable, prefilled automatic injection device which is designed to deliver a single dose of 0.15 mg of epinephrine.

*Keep the EpiPen Jr. Auto-Injector ready for use at all times.

*Protect from exposure to light and extreme heat.

*Note the expiration date on the unit and replace it prior to expiration.

*Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Jr. Auto-Injector is designed with a see-through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

If you experience the signs and symptoms described by your physician, use the EpiPen Jr. Auto-Injector immediately, through clothing if necessary. If you have

been stung by an insect, remove the insect's stinger with your fingernails, if possible; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

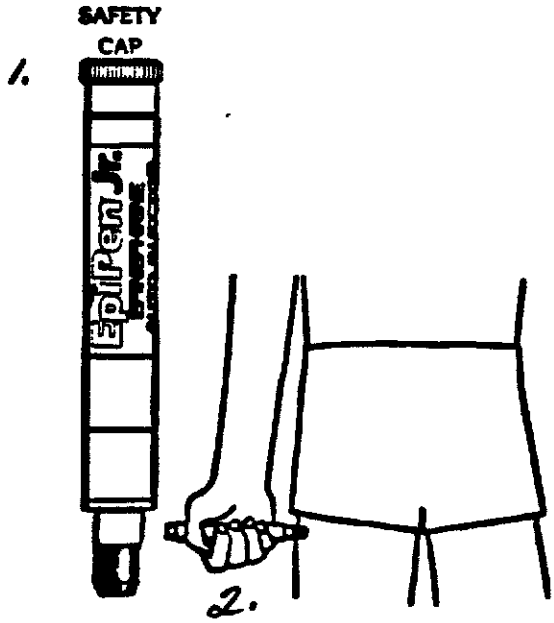
NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen Jr., be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

CONFIDENTIAL

DRAFT
11/2/87

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Always apply to thigh.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



DRAFT
11/2/87

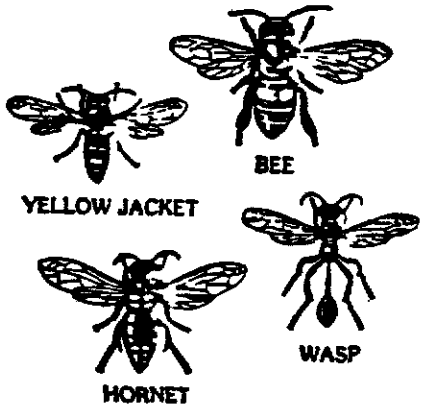
ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

Stinging insects: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



CONFIDENTIAL

(NOT TO SCALE)

-----Tear off here and mail to address shown at bottom-----

EPIPEN AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:

Center Laboratories
EpiPen Alert
35 Channel Drive
Port Washington, NY 11050
U.S.A.

Expiration Date: Lot No.: _____

Name of Purchaser: _____
(Please Print)

Address: _____

City: State: Zip: _____

Date of Purchase: _____

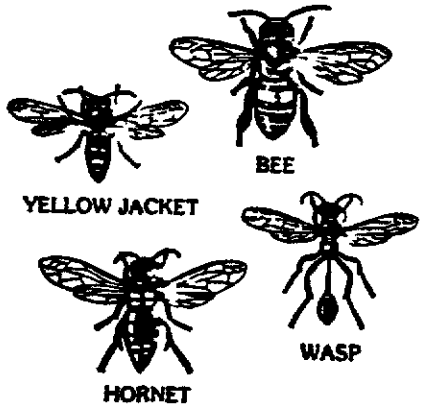
I purchased my EpiPen Auto-Injector at:

Pharmacy Name_____

Address_____

City_____State_____Zip__

MERIDIAN
01597



CONFIDENTIAL

(NOT TO SCALE)

-----Tear off here and mail to address shown at bottom-----

EPIPEN AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:

Center Laboratories
EpiPen Alert
35 Channel Drive
Port Washington, NY 11050
U.S.A.

Expiration Date: Lot No.:

Name of Purchaser:

(Please Print)

Address:

City: State: Zip:

Date of Purchase:

I purchased my EpiPen Auto-Injector at:

Pharmacy Name_____

Address_____

City_____State_____Zip__

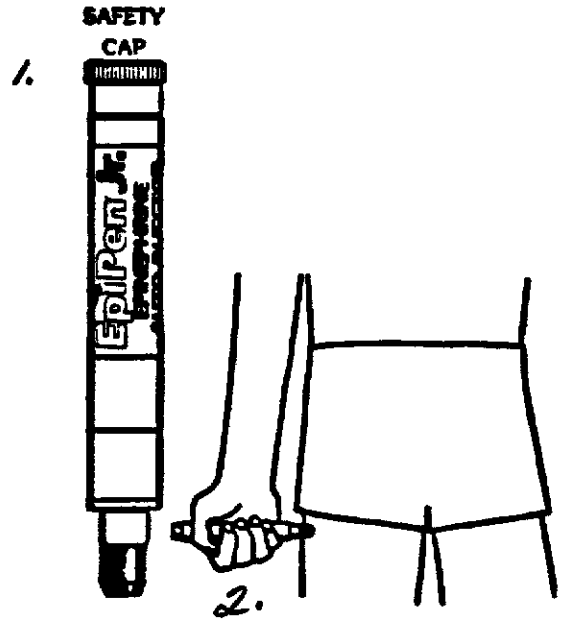
MERIDIAN
01598

DRAFT
11/2/87

CONFIDENTIAL

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh, at right angle to leg (illustration 2). (Always apply to thigh.)
3. Press hard into thigh until Auto-Injector mechanism functions, and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.

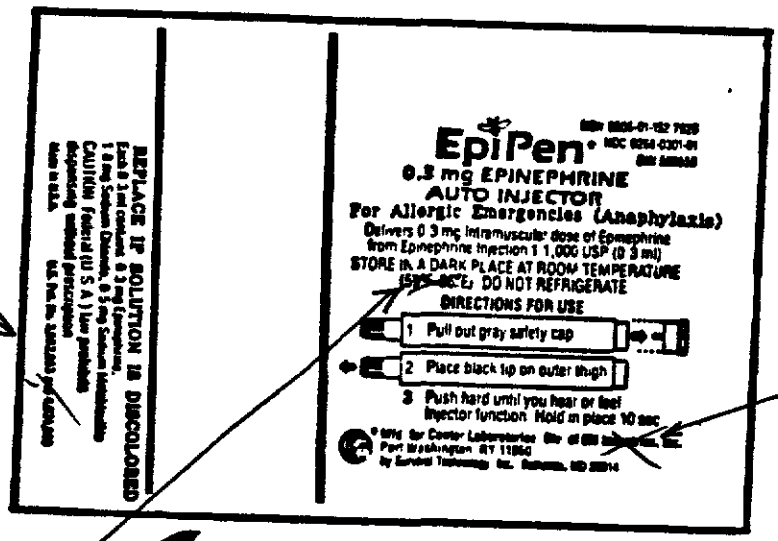


MERIDIAN
01599

5. EPIPEN AND EPIPEN JR. AUTO-INJECTOR LABELS

CONFIDENTIAL

EPIPEN AUTO-INJECTOR LABEL



and 3,712,301

Pharmaceuticals

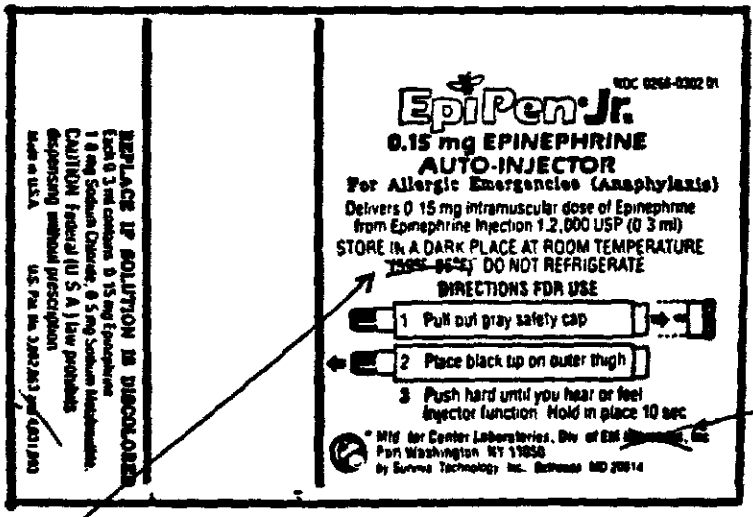
(15°-30°C - 59°-86°F)

Clear Window Area

NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

CONFIDENTIAL

EPIPEN JR. AUTO-INJECTOR LABEL



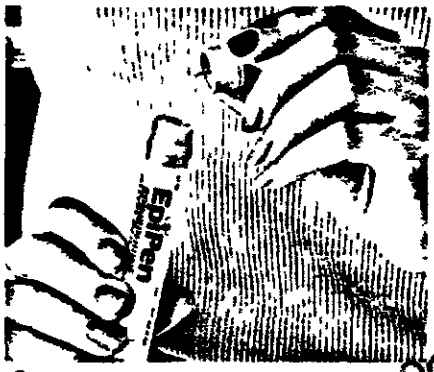
Clear Window Area

NOTE: Expiration Date and Lot Number are Hot Stamped onto Clear Window Area

6. EPIPEN ADS

INSECT STING EMERGENCY TREATMENT

HOW TO USE THE EPIPEN® AUTO-INJECTOR... THREE SIMPLE STEPS:



1. Pull off gray safety cap

2. Place black tip on outer thigh.

3. Push EpiPen® Auto-Injector against thigh until mechanism activates, and hold in place several seconds. Then discard unit

EPIPEN® TRAINER

A re-usable training device is available to facilitate patient instruction and practice of proper EpiPen technique The EpiPen Training Device contains no drug product or needle.

EPIPEN® / EPIPEN® Jr EPINEPHRINE AUTO-INJECTORS

DESCRIPTION The EpiPen® device provides epinephrine for intramuscular auto-injection in a sterile solution prepared from epinephrine with the aid of hydrochloric acid in pyrogen-free water **The EpiPen® Auto-Injector** contains 2 mL Epinephrine Injection 1:1 000 U S P and is designed to deliver a single dose of 0 3 mg epinephrine. Each mL contains Active: 1 00 mg epinephrine Inactive: 6.0 mg sodium chloride, 1 67 mg sodium metabisulfite and hydrochloric acid to adjust pH. **The EpiPen® Jr Auto-Injector** contains 2 mL Epinephrine Injection 1 2 000 U S.P and is designed to deliver a single dose of 0 15 mg epinephrine Each mL contains Active 0.5 mg epinephrine Inactive: 6.00 mg sodium chloride 1 67 mg sodium metabisulfite and hydrochloric acid to adjust pH

CLINICAL PHARMACOLOGY Epinephrine is a sympathomimetic drug acting on both alpha and beta receptors It is the drug of choice for the emergency treatment of severe allergic reactions such as the sting of Hymenoptera insects, bees wasps, hornets and yellow jackets The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability By its effect on smooth muscle epinephrine relaxes the bronchioles, relieving wheezing and dyspnea its action also relieves angioedema or hives

INDICATIONS AND USAGE Epinephrine is indicated in the emergency treatment of anaphylactic reactions to insect stings The EpiPen® and EpiPen® Jr Auto-Injector are intended for immediate self-administration by individuals with a history of hypersensitivity to insect stings. They are designed as emergency supportive therapy only and not as a replacement or substitute for subsequent medical or hospital care nor are they intended to supplant insect venom hyposensitization

CONTRAINDICATIONS Epinphrine is contraindicated in individuals with organic brain damage.

WARNINGS Epinephrine is light sensitive and should be stored in the tube provided. **Store at room temperature (59°F-86°F). Do not refrigerate** Before using check to make sure solution in Auto-Injector is not brown in color If it is discolored or contains a precipitate do not use Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selection of an injection site such as the thigh Do not inject into buttock.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine

Epinephrine should be administered with extreme caution to patients who have developed degenerative heart disease Use of epinephrine with drugs that sensitize the heart to arrhythmias is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

PRECAUTIONS The effects of epinephrine may be potentiated by tricyclic antidepressants certain antihistamines e g diphenhydramine tripelennamine d-chlorpheniramine and sodium 1 thyroxine

Administer with caution to hyperthyroid individuals psychoneurotic individuals, individuals with cardiovascular disease hypertension or diabetes, elderly individuals, pregnant women and children under 30 kg (66 lbs.) body weight.

ADVERSE REACTIONS Transient and minor side effects of epinephrine include palpitation respiratory difficulty, pallor dizziness, weakness tremor headache throbbing restlessness tenseness anxiety and fear Ventricular arrhythmias may follow administration of epinephrine

DOSAGE AND ADMINISTRATION Dosage in any specific patient should be based on body weight in addition to the patient's risk of anaphylaxis and ability to tolerate epinephrine Usual epinephrine adult dosage for allergic emergencies is 0 3 mg Usual pediatric dose is 0 01 mg/kg body weight.

A physician who prescribes EpiPen® or EpiPen® Jr should take appropriate steps to insure that his patient understand the indications and use of the device thoroughly The physician should review with the patient, in detail, the package insert and operation of the Auto-Injector Inject the delivered dose of the Auto-Injector intramuscularly into the anterolateral aspect of the thigh See package insert.

HOW SUPPLIED Package containing one EpiPen® or EpiPen® Jr Auto-Injector and in packages of six units Training Device for patient instruction also available

CAUTION Federal (U S A.) law prohibits dispensing without a prescription

For price information, see current Center Price List in flap on inside back cover of this catalog

CENTER LABS PRODUCT CATALOG AD

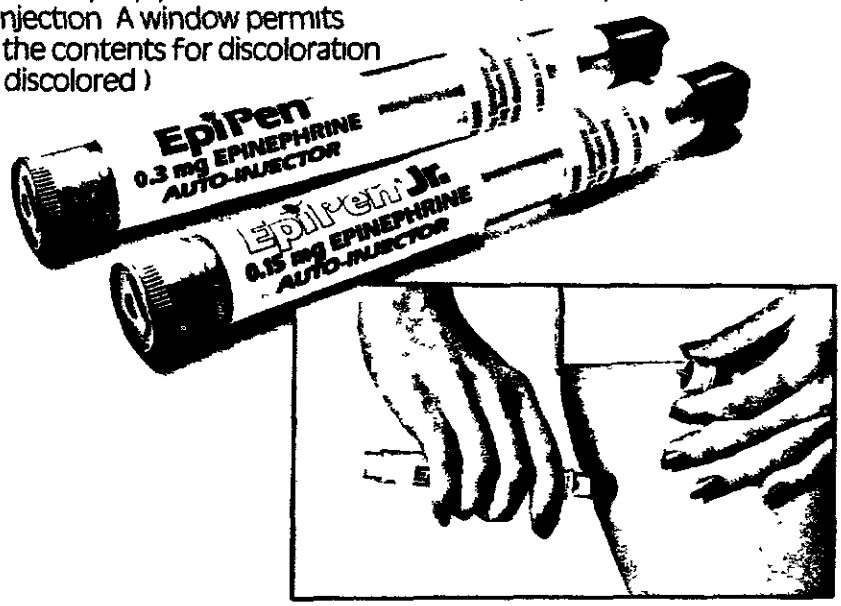
INSECT STING EMERGENCY TREATMENT

EpiPen®/EpiPen® Jr.

EPINEPHRINE AUTO-INJECTORS

These compact, convenient Epinephrine Auto-Injectors are always ready for emergency use, they require no filling, assembly or preparation. The concealed needle minimizes patient apprehension and resistance to self-injection The EpiPen device is activated by a simple push when held against the thigh and instantly delivers the appropriate dose of epinephrine A safety cap prevents accidental discharge or injection A window permits inspection of the contents for discoloration (Do not use if discolored)

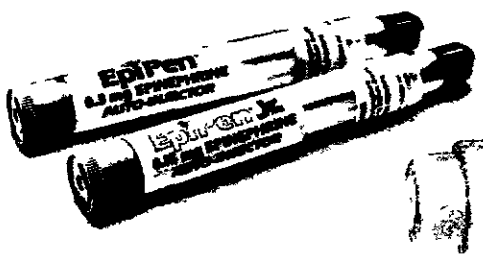
Available in two strengths. EpiPen (yellow label) delivers 0 3 mg Epinephrine 1 1000 EpiPen Jr (white label) delivers 0.15 mg Epinephrine 1·2000 Each EpiPen is packaged with complete instructions for emergency use and helpful suggestions to avoid Hymenoptera stings EpiPen is available at local pharmacies (Caution Federal (U S A) law prohibits dispensing without a prescription)



MERIDIAN
01605

AVAILABLE AT PHARMACIES

Thanks to an EpiPen Epinephrine Auto-Injector, this allergic patient just avoided a serious anaphylactic reaction.



- For Insect Sting Emergencies, fast, reliable First-Aid for hymenoptera-sensitive patients.
- Automatically delivers an accurate premeasured dose of Epinephrine intramuscularly; 0.3 mg (EpiPen®) or 0.15 mg (EpiPen® Jr.).
- Always ready for use; requires no filling, assembly or preparation. Just remove gray safety cap and press hard against thigh.
- Concealed needle minimizes patient fear and resistance to self-injection.
- Virtually painless; penetrates skin with little or no sensation.

For literature and free supply of EpiPen® Rx Pads, please write

Center Laboratories
Division of EM Industries, Inc.

35 Channel Drive, Port Washington, NY 11050-0110
Tel 800-645-6335 In NY 516-767-1800 (call collect).
In CA 800-824-8732. In AZ, ID, NV, OR, UT, WA 800-824-8731
Distributed in Canada by Allerex Laboratories, Montreal, Quebec
Tel 514-489-9306

Manufactured for Center Laboratories by Survival Technology Inc., Bethesda MD 20814
U.S. Patent No. 3,882,863 and 4,031,893

DESCRIPTION The EpiPen® device provides epinephrine for intramuscular auto-injection in a sterile solution prepared from epinephrine with the aid of hydrochloric acid in pyrogen-free water. **The EpiPen® Auto-Injector** contains 2 ml Epinephrine Injection 1:1,000 U.S.P. and is designed to deliver a single dose of 0.3 mg epinephrine. Each ml contains: Active: 1.00 mg epinephrine. Inactive: 6.0 mg sodium chloride, 1.67 mg sodium metabisulfite, and hydrochloric acid to adjust pH. **The EpiPen® Jr Auto-Injector** contains 2 ml Epinephrine Injection 1:2,000 U.S.P. and is designed to deliver a single dose of 0.15 mg epinephrine. Each ml contains: Active: 0.5 mg epinephrine. Inactive: 6.00 mg sodium chloride, 1.67 mg sodium metabisulfite, and hydrochloric acid to adjust pH.

CLINICAL PHARMACOLOGY Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions such as the sting of Hymenoptera insects: bees, wasps, hornets and yellow jackets. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE Epinephrine is indicated in the emergency treatment of anaphylactic reactions to insect stings. The EpiPen® and EpiPen® Jr. Auto-Injector are intended for immediate self-administration by individuals with a history of hypersensitivity to insect stings. They are designed as emergency supportive therapy only and not as a replacement or substitute for subsequent medical or hospital care, nor are they intended to supplant insect venom hyposensitization.

CONTRAINDICATIONS Epinephrine is contraindicated in individuals with organic brain damage.

WARNINGS Epinephrine is light-sensitive and should be stored in the tube provided. **Store at room temperature (59°F-86°F). Do not refrigerate.** Before using, check to make sure solution in Auto-Injector is not brown in color. If it is discolored or contains a precipitate, do not use. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selection of an injection site such as the thigh. Do not inject into buttock.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine should be administered with extreme caution to patients who have developed degenerative heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

PRECAUTIONS The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium l-thyroxine.

Administer with caution to hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women and children under 30 kg (66 lbs.) body weight.

ADVERSE REACTIONS Transient and minor side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessness, tenseness, anxiety and fear. Ventricular arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION Dosage in any specific patient should be based on body weight in addition to the patient's risk of anaphylaxis and ability to tolerate epinephrine. Usual Epinephrine adult dosage for allergic emergencies is 0.3 mg. Usual pediatric dose is 0.01 mg/kg body weight.

A physician who prescribes EpiPen® or EpiPen® Jr. should take appropriate steps to insure that his patient understands the indications and use of the device thoroughly. The physician should review with the patient in detail the package insert and operation of the Auto-Injector. Inject the delivered dose of the Auto-Injector intramuscularly into the anterolateral aspect of the thigh. See package insert.

HOW SUPPLIED Package containing one EpiPen® or EpiPen® Jr. Auto-Injector and in packages of six units. Training Device for patient instruction purposes also available.

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription.

Issued February 1985

MERIDIAN 01606

Survival Technology, Inc.

November 3, 1987

CONFIDENTIAL

NDA 19-430

Division of Drug Advertising and Labeling
HFN 240 Room 10B-04
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir or Madam:

Please refer to our new drug application for EpiPen and EpiPen Jr. Auto-Injectors (epinephrine injection). We are submitting advertising material for your review as requested in the approvable letter dated October 23, 1987 (see enclosures). The material consists of a journal ad and product catalog ad. The full disclosure section of the ads will be replaced with the text from the revised package inserts when approved.

Please call me at (301) 656-5600 if you need any additional information. We look forward to your prompt review of this material.

Sincerely,

Gary W. Leyland
Manager
Clinical and Regulatory Affairs

Enclosures

MERIDIAN
01612

8101 GLENBROOK ROAD • BETHESDA, MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892694 • CABLE SURTECH, BHDA

AVAILABLE AT PHARMACIES

Thanks to an EpiPen Epinephrine Auto-Injector, this allergic patient just avoided a serious anaphylactic reaction.

- For Insect Sting Emergencies, fast, reliable First-Aid for hymenoptera-sensitive patients.
- Automatically delivers an accurate premeasured dose of Epinephrine intramuscularly; 0.3 mg (EpiPen®) or 0.15 mg (EpiPen® Jr.).
- Always ready for use; requires no filling, assembly or preparation. Just remove gray safety cap and press hard against thigh.
- Concealed needle minimizes patient fear and resistance to self-injection.
- *Virtually painless; penetrates skin with little or no sensation.*

For literature and free supply of EpiPen® Rx Pads, please write

Center Laboratories
Division of EM Industries, Inc.
35 Channel Drive, Port Washington, NY 11050-0110
Tel 800-645-6335 In NY 516-767-1800 (call collect).
In CA. 800-824-8732. In AZ, ID, NV, OR, UT, WA. 800-824-8731
Distributed in Canada by Allerex Laboratories, Montreal, Quebec
Tel 514-489-9306
Manufactured for Center Laboratories by Survival Technology, Inc., Bethesda, MD 20814
U.S. Patent No. 3,882,863 and 4,031,893

DESCRIPTION The EpiPen® device provides epinephrine for intramuscular auto-injection in a sterile solution prepared from epinephrine with the aid of hydrochloric acid in pyrogen-free water. The EpiPen® Auto-Injector contains 2 ml Epinephrine Injection 1:1,000 U.S.P. and is designed to deliver a single dose of 0.3 mg epinephrine. Each ml contains: Active: 1.00 mg epinephrine. Inactive: 6.0 mg sodium chloride, 1.67 mg sodium metabisulfite and hydrochloric acid to adjust pH. The EpiPen® Jr. Auto-Injector contains 2 ml Epinephrine Injection 1:2,000 U.S.P. and is designed to deliver a single dose of 0.15 mg epinephrine. Each ml contains: Active: 0.5 mg epinephrine. Inactive: 6.00 mg sodium chloride, 1.67 mg sodium metabisulfite and hydrochloric acid to adjust pH.

CLINICAL PHARMACOLOGY Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions such as the sting of Hymenoptera insects: bees, wasps, hornets, and yellow jackets. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle, epinephrine relaxes the bronchioles, relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE Epinephrine is indicated in the emergency treatment of anaphylactic reactions to insect stings. The EpiPen® and EpiPen® Jr. Auto-Injector are intended for immediate self-administration by individuals with a history of hypersensitivity to insect stings. They are designed as emergency supportive therapy only and not as a replacement or substitute for subsequent medical or hospital care; nor are they intended to supplant insect venom hyposensitization.

CONTRAINDICATIONS Epinephrine is contraindicated in individuals with organic brain damage.

WARNINGS Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (59°F-86°F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not brown in color. If it is discolored or contains a precipitate, do not use. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selection of an injection site such as the thigh. Do not inject into buttock.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine should be administered with extreme caution to patients who have developed degenerative heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

PRECAUTIONS The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheneramine; and thiodiene 1-thyroxine.

Administer with caution to hyperthyroid individuals; psychoneurotic individuals; individuals with cardiovascular disease, hypertension or diabetes, elderly individuals, pregnant women and children under 30 kg (66 lbs.) body weight.

ADVERSE REACTIONS Transient and minor side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessness, tenseness, anxiety and fear. Ventricular arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION Dosage in any specific patient should be based on body weight in addition to the patient's risk of anaphylaxis and ability to tolerate epinephrine. Usual Epinephrine adult dosage for allergic emergencies is 0.3 mg. Usual pediatric dose is 0.01 mg/kg body weight.

A physician who prescribes EpiPen® or EpiPen® Jr. should take appropriate steps to insure that his patient understands the indications and use of the device thoroughly. The physician should review with the patient in detail the package insert and operation of the Auto-Injector. Inject the delivered dose of the Auto-Injector intramuscularly into the anterolateral aspect of the thigh. See package insert.

HOW SUPPLIED Package containing one EpiPen® or EpiPen® Jr. Auto-Injector and in packages of six units. Training Device for patient instruction purposes also available.

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription.

Issued February 1985

MERIDIAN
01613

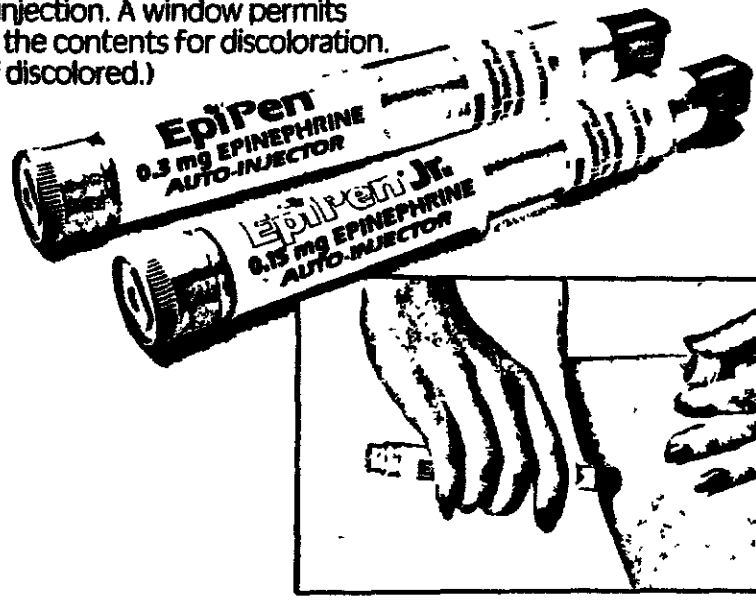
INSECT STING EMERGENCY TREATMENT

EpiPen®/EpiPen® Jr.

EPINEPHRINE AUTO-INJECTORS

These compact, convenient Epinephrine Auto-Injectors are always ready for emergency use; they require no filling, assembly or preparation. The concealed needle minimizes patient apprehension and resistance to self-injection. The EpiPen device is activated by a simple push when held against the thigh and instantly delivers the appropriate dose of epinephrine. A safety cap prevents accidental discharge or injection. A window permits inspection of the contents for discoloration. (Do not use if discolored.)

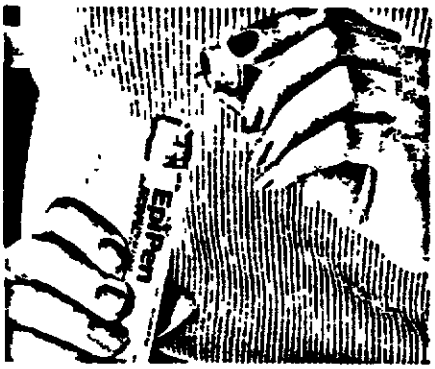
Available in two strengths. EpiPen (yellow label) delivers 0.3 mg Epinephrine 1:1000. EpiPen Jr. (white label) delivers 0.15 mg Epinephrine 1:2000. Each EpiPen is packaged with complete instructions for emergency use and helpful suggestions to avoid Hymenoptera stings. EpiPen is available at local pharmacies. (Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.)



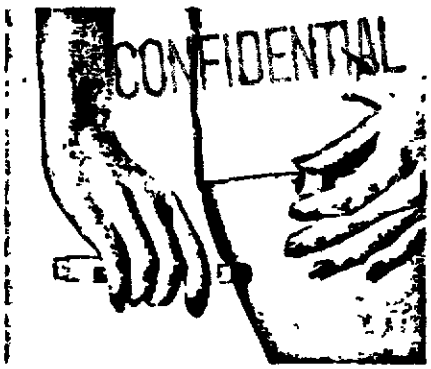
MERIDIAN
01614

INSECT STING EMERGENCY TREATMENT

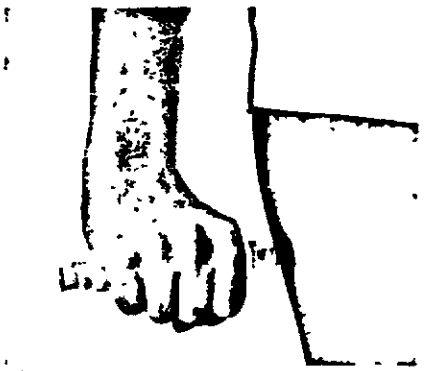
HOW TO USE THE EPIPEN® AUTO-INJECTOR... THREE SIMPLE STEPS:



1. Pull off gray safety cap.



2. Place black tip on outer thigh



3. Push EpiPen® Auto-Injector against thigh until mechanism activates, and hold in place several seconds. Then discard unit.

EPIPEN® TRAINER

A re-usable training device is available to facilitate patient instruction and practice of proper EpiPen technique. The EpiPen Training Device contains no drug product or needle.

EPIPEN® / EPIPEN® Jr. EPINEPHRINE AUTO-INJECTORS

DESCRIPTION The EpiPen® device provides epinephrine for intramuscular auto-injection in a sterile solution prepared from epinephrine with the aid of hydrochloric acid in pyrogen free water. The EpiPen® Auto-Injector contains 2 mL Epinephrine Injection 1:1,000 U.S.P. and is designed to deliver a single dose of 0.3 mg epinephrine. Each mL contains: Active: 1.00 mg epinephrine. Inactive: 6.0 mg sodium chloride, 1.67 mg sodium metabisulfite and hydrochloric acid to adjust pH. The EpiPen® Jr. Auto-Injector contains 2 mL Epinephrine Injection 1:2,000 U.S.P. and is designed to deliver a single dose of 0.15 mg epinephrine. Each mL contains: Active: 0.5 mg epinephrine. Inactive: 6.00 mg sodium chloride, 1.67 mg sodium metabisulfite and hydrochloric acid to adjust pH.

CLINICAL PHARMACOLOGY Epinephrine is a sympathomimetic drug acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions such as the sting of Hymenoptera insects: bees, wasps, hornets, and yellow jackets. The strong vasoconstrictor action of epinephrine acts quickly to counter vasodilation and resulting increased capillary permeability. By its effect on smooth muscle epinephrine relaxes the bronchioles, relieving wheezing and dyspnea. Its action also relieves angioedema or hives.

INDICATIONS AND USAGE Epinephrine is indicated in the emergency treatment of anaphylactic reactions to insect stings. The EpiPen® and EpiPen® Jr. Auto-Injector are intended for immediate self administration by individuals with a history of hypersensitivity to insect stings. They are designed as emergency supportive therapy only and not as a replacement or substitute for subsequent medical or hospital care, nor are they intended to supplant insect venom hyposensitization.

CONTRAINDICATIONS Epinephrine is contraindicated in individuals with organic brain damage.

WARNINGS Epinephrine is light-sensitive and should be stored in the tube provided. **Store at room temperature (59°F-86°F). Do not refrigerate.** Before using, check to make sure solution in Auto-Injector is not brown in color. If it is discolored or contains a precipitate, do not use. Every effort should be made to avoid possible inadvertent intravascular administration through appropriate selection of an injection site such as the thigh. Do not inject into buttock.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine should be administered with extreme caution to patients who have developed degenerative heart disease. Use of epinephrine with drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

PRECAUTIONS The effects of epinephrine may be potentiated by tricyclic antidepressants, certain antihistamines, e.g., diphenhydramine, tripelennamine, d-chlorpheniramine, and sodium-l-thyroxine.

Administer with caution to hyperthyroid individuals, psychoneurotic individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30 kg (66 lbs.) body weight.

ADVERSE REACTIONS Transient and minor side effects of epinephrine include palpitation, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, throbbing, restlessness, tenseness, anxiety and fear. Ventricular arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION Dosage in any specific patient should be based on body weight, in addition to the patient's risk of anaphylaxis and ability to tolerate epinephrine. Usual epinephrine adult dosage for allergic emergencies is 0.3 mg. Usual pediatric dose is 0.01 mg/kg body weight.

A physician who prescribes EpiPen® or EpiPen® Jr. should take appropriate steps to insure that his patient understand the indications and use of the device thoroughly. The physician should review with the patient, in detail, the package insert and operation of the Auto-Injector. Inject the delivered dose of the Auto-Injector intramuscularly into the anterolateral aspect of the thigh. See package insert.

HOW SUPPLIED Package containing one EpiPen® or EpiPen® Jr. Auto-Injector and in packages of six units. Training Device for patient instruction also available.

CAUTION Federal (U.S.A.) law prohibits dispensing without a prescription.

For price information, see current Center Price List in flap on inside back cover of this catalog.

MERIDIAN
01615

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 22 1987

NDA 19-430

CONFIDENTIAL

Survival Technology, Inc.
8101 Glenbrook Road
Bethesda, MD 20814

DEC 28 1987

Attention: Gary Leyland
Manager
Clinical and Regulatory Affairs

Gentlemen:

Please refer to your new drug application dated January 31, 1985, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for the new drug, Epi-Pen and Epi-Pen Jr. Auto-Injector (epinephrine injection).

We also acknowledge your additional communication dated November 2, 1987, amending the application.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate tha the drug product is safe and effective for use as recommended in the submitted draft labeling as revised below. Accordingly, the application, with the labeling revisions described below, is approved effective as of the date of this letter.

The labeling revisions are as follows:

1. In the Description section, your proposed change is not acceptable unless you add additional wording to indicate why 2 ml is used and what happens to the additional 1.7 ml of epinephrine in the Epi-Pen and Epi-Pen Jr.

2. The last sentence in the previously submitted labeling under the Indications and Usage section has been omitted. This sentence which states that, "The Epi-Pen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care," should be re-inserted in this section.

3. The last sentence in the Precautions section should be changed to read, "Therefore, patients with these conditions, and/or any other person who might be in a position to administer Epi-Pen or Epi-Pen Jr. to a patient experiencing anaphylaxis should be...".

4. The Carcinogenesis, Mutagenesis, and Impairment of Fertility section is acceptable with the addition of the following statement, "This should not prevent the use of this life-saving medication under the conditions noted under Indications and Usage and as indicated under Precautions above."

5. The last sentence in the Overdosage section should be removed since the patient's physician will need to assess whether a vasodilator is appropriate given that it may augment hypotension caused by further antigen release.

CONFIDENTIAL

6. Under the Dosage and Administration section on page 9, first paragraph, second line, change "...insure that his patient..." to "...insure that the patient..."

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product a misbranded and unapproved new drug.

Please submit twelve copies of the revised FPL when available. This submission should be designated for administrative purposes as an "FPL Supplement" to the approved NDA 19-430. Approval of the supplement by the FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of that labeling may be required.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Paula Botstein MD

Paula Botstein, M.D.
Deputy Director (Medical Affairs)
Office of Drug Research and Review
Center for Drug Evaluation and Research

FILE

MIKE KROEHNKE
EPIPEN
NDA

Survival Technology, Inc.

CONFIDENTIAL May 17, 1988

NDA 19-430
Philip G. Walters, M.D.
Director
Division of Surgical-Dental Drug Products
HFN 160 Room 18B08
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Walters:

Please refer to our new drug application for EpiPen® and EpiPen® Jr. Auto-Injectors (epinephrine injection), and to the approval letter for this application dated December 22, 1987. We are submitting a final printed labeling supplement to provide copies of revised final printed labeling.

Enclosed are twelve copies each of the following items:

EpiPen Immediate Container Label
EpiPen Patient Instructions
EpiPen Physician's Insert
EpiPen Jr. Immediate Container Label
EpiPen Jr. Patient Instructions
EpiPen Jr. Physician's Insert

Upon examination of the final printed labeling, two minor typographical errors were discovered. On both Patient Inserts, front side, right column, first paragraph, third line, the word "physician" is misspelled. On the EpiPen Jr. Physician's Insert in the "How Supplied" section, the dash between 59°-86° F is missing. The errors will be corrected at the next printing, which is due to occur shortly.

Please call me at 656-5600 if you have any questions.

Sincerely,

Gary W. Leyland

Gary W. Leyland
Director
Regulatory Affairs

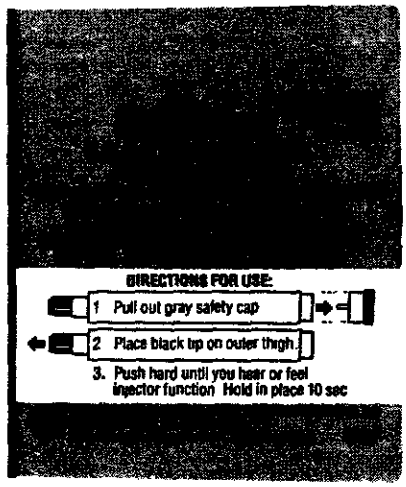
Enclosures

MERIDIAN
01619

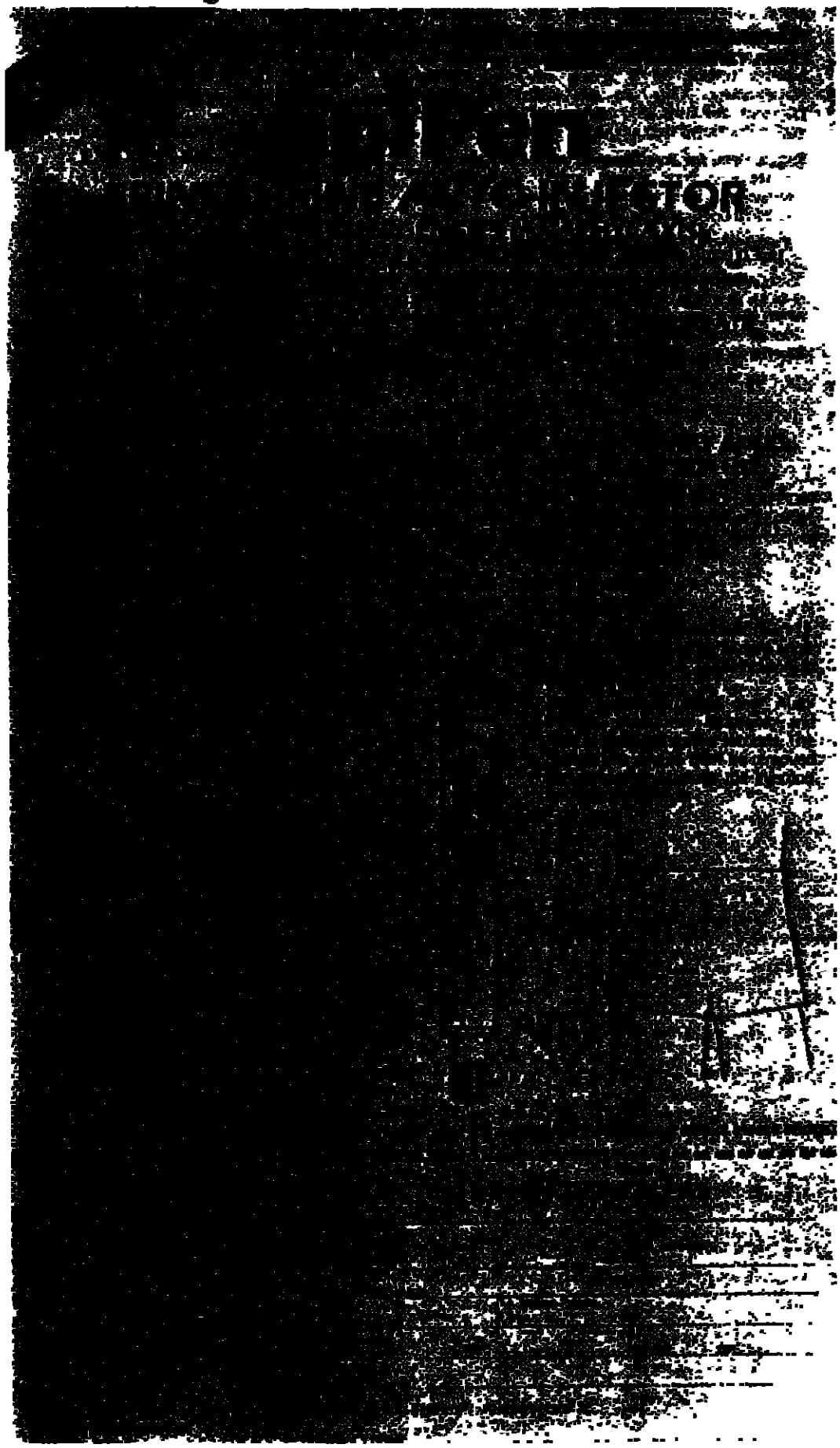
8101 GLENBROOK ROAD • BETHESDA, MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892694 • CABLE SURTECH, BHDA

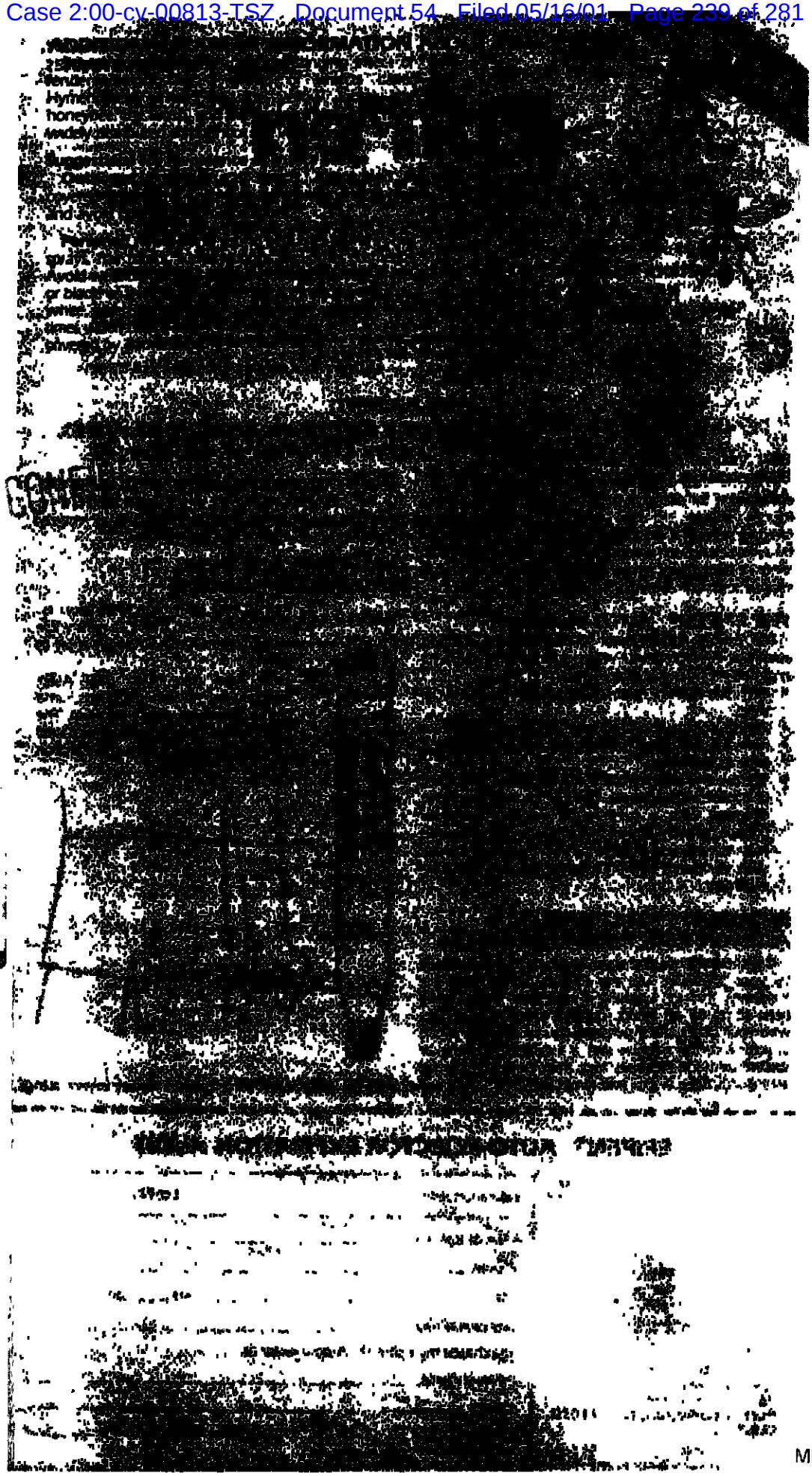
EPIPEN® IMMEDIATE CONTAINER LABEL

CONFIDENTIAL



EPIPEN® PATIENT INSTRUCTIONS





EPIPEN® PHYSICIAN'S INSERT

CONFIDENTIAL

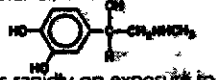
EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0.3 mg Intramuscular dose of epinephrine from Epinephrine Injection USP 1:1000 (0.3 mL)

DESCRIPTION

The EpiPen Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 mL) in a sterile solution. For stability purposes, approximately 1.7 mL remains in the auto-injector after activation. Each 0.3 mL contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5-5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is R-(3, 4-dihydroxyphenyl)-a-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema. The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15°-30°C/59°-86°F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. Select an appropriate injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration (See Dosage and Administration):

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease. Use of epinephrine with drugs that may sensitize the heart to arrhythmias, e.g. digitalis, mercurial diuretics or quinidine, ordinarily is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30 kg (66 lbs.) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr. to a patient experiencing anaphylaxis, should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above.

USAGE IN PREGNANCY

Pregnancy Category C. Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose. There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration).

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety.

Cardiac arrhythmias may follow administration of epinephrine.

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure. Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation.

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly. The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr. to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen Auto-Injector. Inject the delivered dose of the EpiPen Auto-Injector (0.3 mL Epinephrine Injection, USP, 1:1000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. See detailed Directions for Use on the accompanying Patient Instructions.

Usual epinephrine adult dose for allergic emergencies is 0.3 mg. For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient (see labeling for EpiPen Jr.). However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed. The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children.

With severe persistent anaphylaxis, repeat injections with an additional EpiPen may be necessary.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection, USP, 1:1000, 0.3 mL) are available singly or in packages of twelve (pharmacy pack) NDC 0268-0301-01. Store in a dark place at room temperature (15°-30°C/59°-86°F). Do not refrigerate.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc.
35 Channel Drive, Port Washington, NY 11050, U.S.A.
By Survival Technology, Inc., Bethesda MD 20814, U.S.A.

Date of Issue January 1988

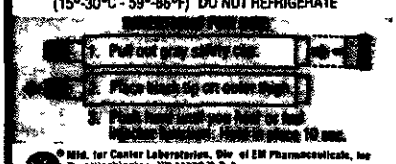
192A

EPIPEN® JR. IMMEDIATE CONTAINER LABEL

CONFIDENTIAL

REPLACE IF SOLUTION IS DISCOLORED
Each 0.3 mL contains: 0.15 mg Epinephrine
1.8 mg Sodium Chloride, 0.5 mg Sodium Metabisulfite
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription
Made in U.S.A.
U.S. Pat. No. 3,882,863 4,031,893 and 3,712,301

EpiPen Jr.
NDC 0268-0302-01
DIN 576657
0.15 mg EPINEPHRINE AUTO-INJECTOR
FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)
Delivers 0.15 mg intramuscular dose of Epinephrine from Epinephrine Injection, USP (0.3 mL)
STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C - 59°-86°F) DO NOT REFRIGERATE



Mfd. for Center Laboratories, Div. of EM Pharmaceuticals, Inc.
Port Washington, NY 11050 U.S.A.
by Survival Technology, Inc. Bethesda, MD 20814 U.S.A.
323B

MERIDIAN
01625

EPIPEN® JR. PATIENT INSTRUCTIONS

CONFIDENTIAL

0.15 mg

NDC 0268-0302-01
DIN 578657

LOT XXXXXX
EXP XXX XX

READ INSTRUCTIONS CAREFULLY, BEFORE AN EMERGENCY ARISES.

EpiPen® Jr.

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0 15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION USP 1 2000 (0 3mL)

Caution: Federal (U S A) law prohibits dispensing without a prescription

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C/59°-86°F). DO NOT REFRIGERATE.

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc.,
Port Washington, NY 11050 U.S.A.
by Survival Technology Inc Bethesda MD 20814 U S A US Patent No 3 882 863 4 031 893 and 3 712 301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.
IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies The EpiPen Jr Auto-Injector should be used only by a hypersensitive (allergic) person in the event of an allergic emergency as prescribed by a physician Such emergencies may occur from insect stings or bites foods, drugs or other allergens as well as idiopathic or exercise-induced anaphylaxis

THE EPIPEN® JR. AUTO-INJECTOR

The EpiPen Jr Auto-Injector is a disposable prefilled automatic injection device which is designed to deliver a single dose of 0 15 mg of epinephrine

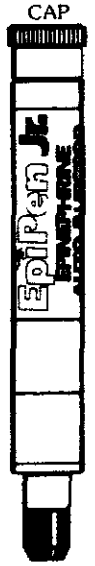
- Keep the EpiPen Jr Auto-Injector ready for use at all times
- Protect from exposure to light and extreme heat
- Note the expiration date on the unit and replace it prior to expiration
- *Replace any auto-injector if the solution is discolored* or contains a precipitate The EpiPen Jr Auto-Injector is designed with a see-through window to allow periodic examination of its contents The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment

EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

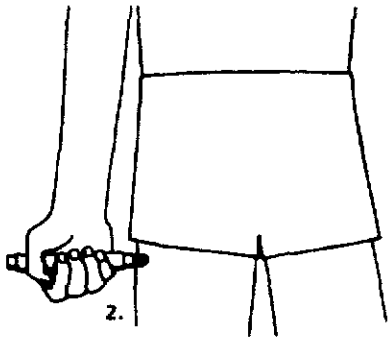
If you experience the signs and symptoms described by your physician use the EpiPen Jr Auto-Injector immediately through clothing if necessary If you have been stung by an insect remove the insect's stinger with your fingernails if possible do not squeeze pinch or push it deeper into the skin If available ice packs or sodium bicarbonate soaks may then be applied to the area stung Keep warm and avoid exertion

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL If you have used EpiPen Jr be sure to explain to the phyician that you have received an intramuscular injection of epinephrine

DIRECTIONS FOR USING EPIPEN JR. AUTO-INJECTOR



1. Pull off gray safety cap (illustration 1)
2. Place black tip on thigh at right angle to leg (illustration 2) (Always apply to thigh)
3. Press hard into thigh until Auto-Injector mechanism functions and hold in place for several seconds The EpiPen unit should then be removed and discarded Massage the injection area for 10 seconds



See other side for additional information about insect stings

Tear off here and mail to address shown at bottom

MERIDIAN
01626

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
Center Laboratories
EpiPen Alert
35 Channel Drive
Port Washington, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____
(Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

CONFIDENTIAL

Date of Issue January 1988
195A

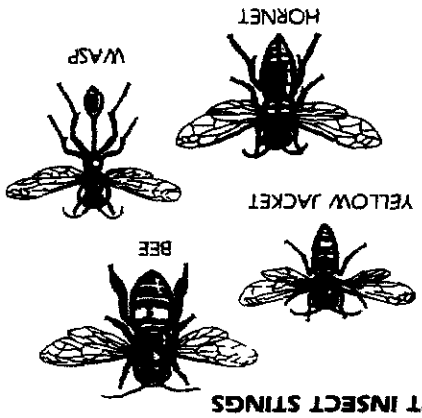
ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

Stinging Insects The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp and the hornet. These insects are widely distributed throughout the world.

Suggestions for Avoidance of Insect Stings

Outdoors: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

Personal. Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints or black, as this color seems to attract insects more than white, green, tan or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



MERIDIAN
01627

EPIPEN® JR. PHYSICIAN'S INSERT

CONFIDENTIAL

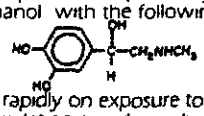
EPIPEN® JR. 0.15 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0 15 mg intramuscular dose of epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL)

DESCRIPTION

The EpiPen Jr Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use Each EpiPen Jr Auto-Injector delivers a single dose of 0 15 mg epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL) in a sterile solution For stability purposes approximately 1 7 mL remains in the auto-injector after activation Each 0 3 mL contains 0 15 mg epinephrine 1 8 mg sodium chloride 0 5 mg sodium metabisulfite hydrochloric acid to adjust pH, and Water for Injection The pH range is 2 5-5 0

Epinephrine is a sympathomimetic catecholamine *Chemically epinephrine is B-(3 4 dihydroxyphenyl)-a* methylaminoethanol with the following structure



It deteriorates rapidly on exposure to air or light turning pink from oxidation to adrenochrome and brown from the formation of melanin EpiPen Jr Auto-Injectors *whose contents show evidence of discoloration should* be replaced

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug acting on both alpha and beta receptors It is the drug of choice for *the emergency treatment of severe allergic reactions* (Type I) to insect stings or bites foods drugs and other allergens It can also be used in the treatment of idiopathic or exercise induced anaphylaxis Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions Epinephrine *through its action on beta receptors on bronchial* smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea Epine*phrine also alleviates pruritis urticaria and angioedema* and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites foods drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis The EpiPen Jr Auto Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction Such reactions may occur within minutes after exposure and consist of flushing apprehension syncope tachycardia, thready or unobtainable pulse associated with a fall in blood pressure convulsions vomiting diarrhea and abdominal cramps involuntary voiding *wheezing dyspnea due to laryngeal spasm pruritis* rashes urticaria or angioedema The EpiPen is designed as emergency supportive therapy only and is not a *replacement or substitute for immediate medical or* hospital care

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation

WARNINGS

Epinephrine is light sensitive and should be stored in *the tube provided Store at room temperature* (15°-30°C/59°-86°F) Do not refrigerate Before using check to make sure solution in Auto-Injector is not discolored Replace the Auto-Injector if the solution is discolored or contains a precipitate Avoid possible inadvertent intravascular administration Select an appropriate injection site such as the thigh DO NOT INJECT INTO BUTTOCK

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure DO NOT INJECT IN*TRAVENOUSLY Rapidly acting vasodilators can* counteract the marked pressor effects of epinephrine

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons The alternatives to using epinephrine in a life-threatening situation may not be satisfactory The presence of a sulfite in this product should not deter administration of *the drug for treatment of serious allergic or other* emergency situations

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis Patients with a history of severe allergic *reactions (anaphylaxis) to insect stings or bites foods* drugs and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used It must be clearly determined that the patient is at risk of future anaphylaxis since the following risks may be associated with epinephrine administration (See Dosage and Administration)

CONFIDENTIAL

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias e g digitalis mercurial diuretics or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors

Hyperthyroid individuals individuals with cardiovascular disease hypertension or diabetes elderly individuals pregnant women and children under 15 kg (33 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration

Despite these concerns epinephrine is essential for the treatment of anaphylaxis Therefore patients with these conditions and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration)

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations tachycardia sweating nausea and vomiting respiratory difficulty pallor dizziness weakness tremor headache apprehension nervousness and anxiety

Cardiac arrhythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly The physician should review with the patient or any other person who might be in a position to administer EpiPen Jr to a patient experiencing anaphylaxis in detail the patient instructions and operation of the EpiPen Jr Auto-Injector Inject the delivered dose of the EpiPen Jr Auto-Injector (0 3 mL Epinephrine Injection USP 1 2000) intramuscularly into the anterolateral aspect of the thigh through clothing if necessary See detailed Directions for Use on the accompanying Patient Instructions

Usual epinephrine adult dose for allergic emergencies is 0 3 mg For pediatric use the appropriate dosage may be 0 15 or 0 30 mg depending upon the body weight of the patient (0 01 mg/Kg body weight) However the prescribing physician has the option of prescribing more or less than these amounts based on careful assessment of each individual patient and recognizing the life threatening nature of the reactions for which this drug is being prescribed The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children

With severe persistent anaphylaxis repeat injections with an additional EpiPen Jr may be necessary

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present

HOW SUPPLIED

EpiPen Jr Auto-Injectors (Epinephrine Injection USP 1 2000 0 3 mL) are available singly or in packages of twelve (pharmacy pack) NDC 0268-0302-1 Store in a dark place at room temperature (15°-30°C/59°86°F) Do not refrigerate

Caution: Federal (U S A) law prohibits dispensing without a prescription

Manufactured for Center Laboratories, Division of EM Pharmaceuticals, Inc
35 Channel Drive, Port Washington, NY 11050, U S A
By Survival Technology Inc Bethesda MD 20814 U S A

Date of Issue January 1988

193A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430

Survival Technology, Inc.
8101 Glenbrook Road
Bethesda, MD 20814

JUN 1 5 1988

Attention: Gary W. Leyland
Director
Regulatory Affairs

Gentlemen:

Please refer to your new drug application dated January 31, 1985, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the new drug, Epi-Pen and Epi-Pen Jr. Auto-Injector (epinephrine injection).

We also acknowledge your additional communication dated May 17, 1988, providing final printed labeling as requested in the approval letter for this application dated December 22, 1987.

This final printed labeling is being retained as part of your application.

Sincerely yours,

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430

SEP 6 1988

Survival Technology, Inc.
8101 Glenbrook Road
Bethesda, MD 20814

SEP 08 1988

Attention: Gary W. Leyland
Director
Regulatory Affairs

Gentlemen:

Please refer to your approved new drug application for Epi-Pen and Epi-Pen Jr. Auto-Injector (epinephrine injection).

We have received two (2) reports of accidental injection of Epi-Pen into the fingers with potential loss of these digits due to decreased blood supply from vasoconstriction. Therefore, we are requesting that the labeling be changed to alert the patient and physician to this possible adverse event. In this regard, an addition to the WARNINGS section should read, "Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. Epi-Pen should only be injected into the thigh or upper arm at the sites indicated in the drawing below." You should prepare a drawing of the areas where it would be appropriate for Epi-Pen to be injected.

This labeling change should be implemented during the next printing and submitted as a supplemental application to this NDA.

Sincerely yours,

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Survival Technology, Inc.

February 13, 1989

CONFIDENTIAL

NDA 19-430
Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental Drug Products
HFN 160, Room 18B03
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

Dear Dr. Walters:

Please refer to our approved new drug application for EpiPen and Epi-Pen Jr. Auto-injectors (epinephrine injection).

We are submitting a labeling supplement in response to your letter of September 6, 1988 in which you requested labeling changes to alert the patient and physician to possible accidental injection into digits.

To comply with this request, the following changes were made:

PHYSICIANS' INSERTS: Paragraph inserted at end of "Warnings" section - "Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, advise the patient to go immediately to the nearest emergency room for treatment. EpiPen should only be injected into the anterolateral aspect of the thigh."

PATIENTS' INSERTS: Sketch and paragraph inserted at end of "Directions For Using" section - "WARNING - Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. EpiPen should only be injected into the thigh as indicated in the drawing below."

Twelve copies each of the four inserts are attached.

Please call me at (301) 656-5600 if there are any questions. Thank you for your cooperation.

Yours truly,

Iantha Peterson

Iantha Peterson
Senior Regulatory Specialist

cc: Gary Leyland - Director of Regulatory Affairs

MERIDIAN
01633

6101 GLENBROOK ROAD • BETHESDA MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892694 • CABLE SURTECH, BHDA

PHYSICIAN INSERT

(PHARMACIST - PLEASE REMOVE BEFORE DISPENSING)

CONFIDENTIAL

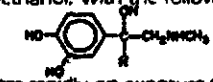
EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0.3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 mL)

DESCRIPTION

The EpiPen Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 mL) in a sterile solution. For stability purposes, approximately 1.7 mL remains in the auto-injector after activation. Each 0.3 mL contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5-5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is R-(3, 4-dihydroxyphenyl)-a-methylaminoethanol, with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema. The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15°-30°C/59°-86°F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. Select an appropriate injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, advise the patient to go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the anterolateral aspect of the thigh.

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and

exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used It must be clearly determined that the patient is at risk of future anaphylaxis since the following risks may be associated with epinephrine administration (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias e g , digitalis, mercurial diuretics or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors

Hyperthyroid individuals individuals with cardiovascular disease hypertension or diabetes, elderly individuals, pregnant women, and children under 30 kg (66 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis Therefore patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration)

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting respiratory difficulty, pallor dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety

Cardiac arrhythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen Auto-Injector Inject the delivered dose of the EpiPen Auto-Injector (0 3 mL Epinephrine Injection USP, 1 1000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary See detailed Directions for Use on the accompanying Patient Instructions

Usual epinephrine adult dose for allergic emerg es is 0 3 mg For pediatric use, the appropriate dosage may be 0 15 or 0 30 mg depending upon the body weight of the patient (see labeling for EpiPen Jr) However the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children

With severe persistent anaphylaxis, repeat injections with an additional EpiPen may be necessary

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection USP, 1 1000 0 3 mL) are available singly or in packages of twelve (pharmacy pack), NDC 0268-0301-01 Store in a dark place at room temperature (15°-30°C/59°-86°F) Do not refrigerate

CAUTION: Federal (U.S.A) law prohibits dispensing without a prescription

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC.
35 CHANNEL DRIVE, PORT WASHINGTON, NY 11050, U.S.A.
By Survival Technology, Inc , Bethesda, MD 20814, U S.A

Date of Issue November 1988

192B

PHYSICIAN INSERT

(PHARMACIST - PLEASE REMOVE BEFORE DISPENSING)

CONFIDENTIAL

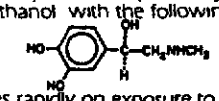
EPIPEN® JR. 0.15 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0 15 mg intramuscular dose of epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL)

DESCRIPTION

The EpiPen Jr Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use Each EpiPen Jr Auto-Injector delivers a single dose of 0 15 mg epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL) in a sterile solution For stability purposes approximately 1 7 mL remains in the auto-injector after activation Each 0 3 mL contains 0 15 mg epinephrine 1 8 mg sodium chloride 0 5 mg sodium metabisulfite hydrochloric acid to adjust pH and Water for Injection The pH range is 2 5-5 0

Epinephrine is a sympathomimetic catecholamine Chemically epinephrine is 8-(3 4-dihydroxyphenyl)-a-methylaminoethanol with the following structure



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown fro the formation of melanin EpiPen Jr Auto-Injectors w contents show evidence of discoloration should be replaced

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug acting on both alpha and beta receptors It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites foods drugs, and other allergens It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea Epinephrine also alleviates pruritis urticaria and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites foods drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis The EpiPen Jr Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction Such reactions may occur within minutes after exposure and consist of flushing, apprehension syncope tachycardia thready or unobtainable pulse associated with a fall in blood pressure convulsions, vomiting diarrhea and abdominal cramps, involuntary voiding wheezing dyspnea due to laryngeal spasm pruritis rashes, urticaria or angioedema The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided Store at room temperature (15°-30°C/59°-86°F) Do not refrigerate Before using check to make sure solution in Auto-Injector is not discolored Replace the Auto-Injector if the solution is discolored or contains a precipitate Avoid possible inadvertent intravascular administration Select an appropriate injection site such as the thigh DO NOT INJECT INTO BUTTOCK

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure DO NOT INJECT INTRAVENOUSLY Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons The alternatives to using epinephrine in a life-threatening situation may not be satisfactory The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided If there is an accidental injection into these areas advise the patient to go immediately to the nearest emergency room for treatment EpiPen should **only** be injected into the anterolateral aspect of the thigh

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites foods, drugs and other allergens as well as idiopathic and

exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used It must be clearly determined that the patient is at risk of future anaphylaxis since the following risks may be associated with epinephrine administration (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias e g digitalis mercurial diuretics or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors

Hyperthyroid individuals individuals with cardiovascular disease hypertension or diabetes elderly individuals pregnant women and children under 15 kg (33 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration

Despite these concerns epinephrine is essential for the treatment of anaphylaxis Therefore patients with these conditions and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration)

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations tachycardia sweating nausea and vomiting, respiratory difficulty pallor, dizziness weakness tremor headache apprehension nervousness and anxiety

Cardiac arrhythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly The physician should review with the patient or any other person who might be in a position to administer EpiPen Jr to a patient experiencing anaphylaxis in detail the patient instructions and operation of the EpiPen Jr Auto Injector Inject the delivered dose of the EpiPen Jr Auto-Injector (0 3 mL Epinephrine Injection USP 1 2000) intramuscularly into the anterolateral aspect of the thigh through clothing if necessary See detailed Directions for Use on the accompanying Patient Instructions

Usual epinephrine adult dose for allergic emerg s is 0 3 mg For pediatric use the appropriate dosage . ay be 0 15 or 0 30 mg depending upon the body weight of the patient (0 01 mg/kg body weight) However the prescribing physician has the option of prescribing more or less than these amounts based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children

With severe persistent anaphylaxis repeat injections with an additional EpiPen Jr may be necessary

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present

HOW SUPPLIED

EpiPen Jr Auto-Injectors (Epinephrine Injection, USP 1 2000 0 3 mL) are available singly or in packages of twelve (pharmacy pack) NDC 0268-0302-1 Store in a dark place at room temperature (15°-30° C/59°-86°F) Do not refrigerate

CAUTION: Federal (U S A) law prohibits dispensing without a prescription

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC.
35 CHANNEL DRIVE, PORT WASHINGTON, NY 11050, U.S.A.
By Survival Technology, Inc , Bethesda, MD 20814 U S A
Date of Issue November 1988

1938

PATIENT INSERT

(PHARMACIST - PLEASE DISPENSE WITH PRODUCT)

0.3 mg

NDC 0268-0301-01
DIN 509558
NSN 6505-01-152-7626

READ INSTRUCTIONS CAREFULLY, BEFORE AN EMERGENCY ARISES.

EpiPen®

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0 3 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION USP 1 1000 (0 3mL)

CAUTION: Federal (U S A) law prohibits dispensing without a prescription

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C/59°-86°F). DO NOT REFRIGERATE.

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC.,
PORT WASHINGTON, NY 11050 U S.A.
by Survival Technology Inc Bethesda MD 20814 U S.A
US Patent No 3 882 863 4 031 893 and 3 712 301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.
IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies The EpiPen Auto-Injector should be used only by a hypersensitive (allergic) person in an allergic emergency as prescribed by a physician Such emergencies may occur from insect stings or bites, foods, drugs or other allergens as well as idiopathic or exercise-induced anaphylaxis

THE EPIPEN® AUTO-INJECTOR

The EpiPen Auto-Injector is a disposable prefilled automatic injection device which is designed to deliver a single dose of 0 3 mg of epinephrine

- *Keep the EpiPen Auto-Injector ready for use at all times*
- *Protect from exposure to light and extreme heat*
- Note the expiration date on the unit and replace it prior to expiration
- Replace any auto-injector if the solution is discolored or contains a precipitate The EpiPen Auto-Injector is designed with a see-through window to allow periodic examination of its contents The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment

EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

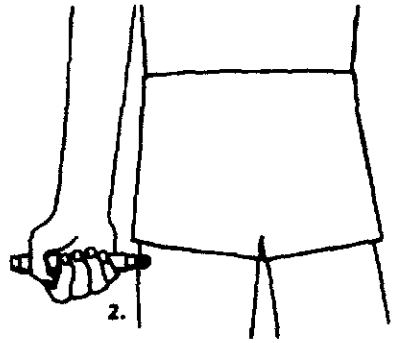
If you experience the signs and symptoms described by your physician use the EpiPen Auto-Injector immediately, through clothing if necessary If you have been stung by an insect remove the insect's stinger with your fingernails if possible, do not squeeze pinch or push it deeper into the skin If available ice packs or sodium bicarbonate soaks may then be applied to the area stung Keep warm and avoid exertion

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL If you have used EpiPen be sure to explain to the physician that you have received an intramuscular injection of epinephrine

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

1. SAFETY CAP

1. Pull off gray safety cap (illustration 1)
2. *Place black tip on thigh at right angle* to leg (illustration 2) (Always apply to *thigh)*
3. Press hard into thigh until Auto-Injector *mechanism functions, and* hold in place for several seconds The *EpiPen unit should then be removed* and discarded Massage the injection area for *10* seconds



SEE OTHER SIDE FOR ADDITIONAL INFORMATION ABOUT INSECT STINGS.

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
CENTER LABORATORIES
EPIPEN ALERT
35 CHANNEL DRIVE
PORT WASHINGTON, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____
(Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at:

PHARMACY NAME _____

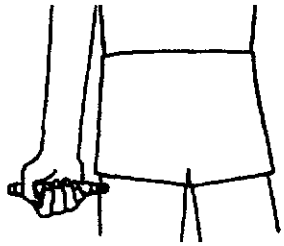
ADDRESS _____

CITY _____ STATE _____ ZIP _____

Tear off here and mail to address shown at bottom

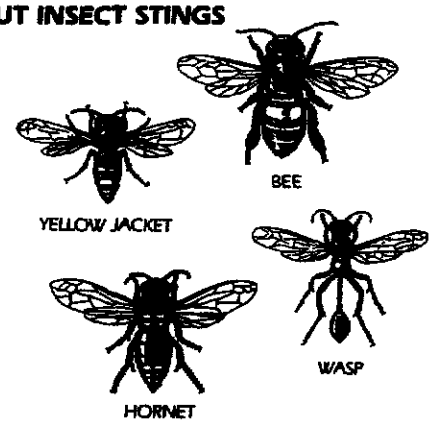
WARNING

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the thigh as indicated in the drawing below.



ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

STINGING INSECTS: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.



SUGGESTIONS FOR AVOIDANCE OF INSECT STINGS

OUTDOORS: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

PERSONAL: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.

Date of Issue November 1

PATIENT INSERT

(PHARMACIST - PLEASE DISPENSE WITH PRODUCT)

NDC 0268-0302-01
DIN 578657

READ INSTRUCTIONS CAREFULLY, BEFORE AN EMERGENCY ARISES

EpiPen® Jr.

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION USP 1:2000 (0.3mL)

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C/59°-86°F). DO NOT REFRIGERATE.

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC., PORT WASHINGTON, NY 11050 U.S.A.
by Survival Technology Inc. Bethesda MD 20814 U.S.A.
US Patent No. 3,882,863 4,031,893 and 3,712,301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.

IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Jr. Auto-Injector should be used only by a hypersensitive (allergic) person in the event of an allergic emergency as prescribed by a physician. Such emergencies may occur from insect stings or bites, foods, drugs or other allergens as well as idiopathic or exercise-induced anaphylaxis.

THE EPIPEN® JR. AUTO-INJECTOR

The EpiPen Jr. Auto-Injector is a disposable prefilled automatic injection device which is designed to deliver a single dose of 0.15 mg of epinephrine.

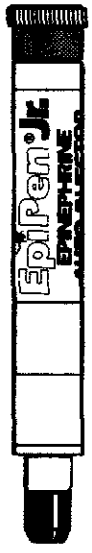
- Keep the EpiPen Jr. Auto-Injector ready for use at all times.
- Protect from exposure to light and extreme heat.
- Note the expiration date on the unit and replace it prior to expiration.
- Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Jr. Auto-Injector is designed with a see-through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

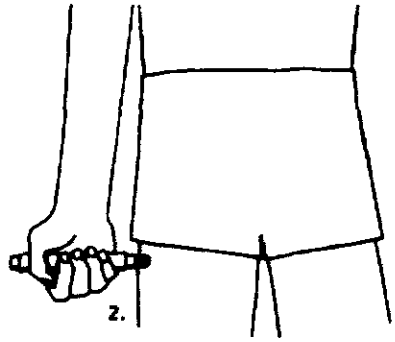
If you experience the signs and symptoms described by your physician, use the EpiPen Jr. Auto-Injector immediately through clothing if necessary. If you have been stung by an insect, remove the insect's stinger with your fingernails, if possible; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen Jr., be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN JR. AUTO-INJECTOR



1. Pull off gray safety cap (illustration 1).
2. Place black tip on thigh at right angle to leg (illustration 2). (Always apply to thigh.)
3. Press hard into thigh until Auto-Injector mechanism functions and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



SEE OTHER SIDE FOR ADDITIONAL INFORMATION ABOUT INSECT STINGS.

MERIDIAN
01640

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
CENTER LABORATORIES
EPIPEN ALERT
35 CHANNEL DRIVE
PORT WASHINGTON, N.Y. 11050
U.S.A.

Expiration date _____ Lot No. _____

NAME OF PURCHASER _____
(Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

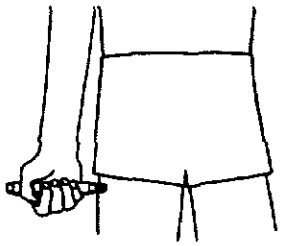
ADDRESS _____

CITY _____ STATE _____ ZIP _____

Tear off here and mail to address shown at bottom

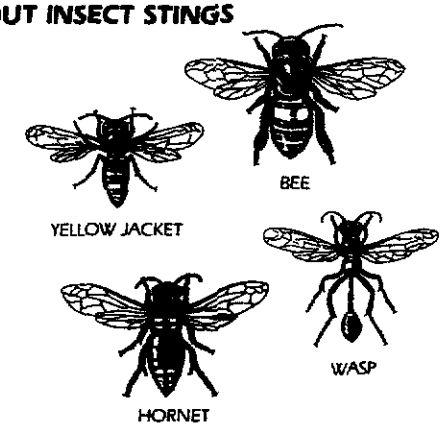
WARNING

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the thigh as indicated in the drawing below.



ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

STINGING INSECTS. The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp and the hornet. These insects are widely distributed throughout the world.



SUGGESTIONS FOR AVOIDANCE OF INSECT STINGS

OUTDOORS: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

PERSONAL: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.

Date of Issue: November 1958

MERIDIAN
01641

MAR 03 1989

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430/S-001

MAR 02 1989

Survival Technology, Inc.
8101 Glenbrook Road
Bethesda, MD 20814

Attention: Ianthana Peterson
Senior Regulatory Specialist

Gentlemen:

Please refer to your supplemental new drug application dated February 13, 1989, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for EpiPen and EpiPen Jr. Auto-injectors (epinephrine injection).

The supplemental application provides for a change in the WARNINGS section of the package insert to alert the patient and physician to possible accidental injection into digits (S-001).

We have completed our review of the supplemental application and it is approved. We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for approved new drugs.

Sincerely yours,

Philip G. Walters

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Epi NDA update box E

Survival Technology, Inc.

February 27, 1990 CONFIDENTIAL

Mr. William Purvis
Division of Drug Advertising and Labeling
HFD-240 Room 10B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Purvis:

We are submitting a revised draft of our proposed EpiPen® Auto-Injector patient education brochure. Changes have been made to reflect your telephone comments of February 20, 1990. These include the addition of text concerning the proper injection site as well as sites to avoid, a brief description of some anticipated drug effects, and inclusion of the complete package insert.

As a result of our previous discussion, we have withdrawn the brochure that was originally submitted to the Pulmonary and Oncology Drugs Division. This action was discussed with Deborah Yaplee, the CSO for EpiPen, and a withdrawal letter was sent to Dr. Gregory Burke, the Division Director, on February 21, 1990.

We appreciate your prompt review of the enclosed material. Please call me at 301-656-5600 if you have any questions.

Sincerely,

Gary W. Leyland
Director
Clinical and Regulatory Affairs

Enclosure

MERIDIAN
01646

8101 GLENBROOK ROAD • BETHESDA, MARYLAND 20814 • TELEPHONE (301) 656-5600
TELEX 892694 • CABLE SURTECH BHDA

DRAFT

CONFIDENTIAL

For
All
Allergic
Emergencies

Revised 2/ 26/ 90

DRAFT

For
All
Allergic
Emergencies

DRAFT

Some Questions
and Answers About
the EpiPen Auto-Injector
For Allergic Emergencies

EpiPen® Auto-Injector, 0.3 mg Epinephrine
EpiPen® Jr. Auto-Injector, 0.15 mg Epinephrine

1. What is the EpiPen® Auto-Injector?

The EpiPen® Auto-Injector is a disposable drug delivery system with a spring-activated, concealed needle. It is designed for emergency self-administration to provide rapid, convenient first-aid for individuals prone to potentially fatal allergic reactions.

2. What is the active ingredient of the EpiPen® Auto-Injector?

The active ingredient is epinephrine. Injection of epinephrine is the treatment of choice for allergic emergencies (anaphylactic reactions) because it quickly constricts blood vessels, relaxes smooth muscles in the lungs to improve breathing, stimulates the heartbeat, and works to reverse hives and swelling around the face and lips (angioedema).

3. Why might I need an EpiPen® Auto-Injector?

The EpiPen is commonly prescribed for individuals who have had prior severe allergic reactions to certain foods such as nuts, shellfish, eggs, etc. or certain food additives; to drugs such as penicillin; to stings by bees, wasps, hornets, yellow jackets, etc.; or to exercise. Such an allergic reaction may be so severe as to be life-threatening and could occur when no physician or hospital is near. With an EpiPen, an emergency injection of epinephrine can be immediately available.

4. Why was the EpiPen® Auto-Injector developed?

Initially this auto-injector design was developed for the military to deliver antidotes in the event of poison gas attack. It was ideal because of the need for a fast, convenient, easy method of giving life-saving medication in a high stress situation. Subsequently, the same auto-injector system was used with other drugs as part of the NASA Manned Space Flight Program. The EpiPen® Auto-Injector resulted from the realization that patients experiencing serious allergic reactions may also be fearful of injecting themselves with life-saving medication or incapable of using a conventional syringe.

5. How does the EpiPen® Auto-Injector work?

The EpiPen is simple to use and the absence of a visible needle helps to minimize fear and resistance to self-injection. Activate the EpiPen by removing the gray safety cap. Hold the EpiPen with the black tip against the thigh, and apply moderate pressure. Pushing the EpiPen against the thigh releases a spring activated plunger, pushing the concealed needle into the thigh muscle and injecting a dose of epinephrine.

6. Where should the EpiPen be placed for injection?

The EpiPen should simply be pushed against the fleshy outer portion of the thigh. There is no need for more precise placement. Do not attempt injection into a vein or into the buttocks.

7. What will I feel when I use an EpiPen® Auto-Injector?

The injection itself is actually quite painless. Upon removing the EpiPen after injection, you will see a short needle protruding. In most instances, the beneficial effects of the drug will be felt within seconds. The most common changes you may feel are a more rapid heart beat and a slight nervousness, "like a shot of adrenalin".

Even though a residual amount of material remains within an EpiPen after use, the unit cannot be used again and should be properly discarded.

8. Can the EpiPen® Auto-Injector be used through clothing?

Yes, if necessary. The preferred method is to remove your clothing from the site of injection. However, if this is too difficult or awkward, or if there is no time, the EpiPen may be used directly through your clothing.

9. Does the EpiPen® Auto-Injector come in different strengths?

Yes. EpiPen® Auto-Injectors come in two strengths: 0.3 mg (Yellow Label) and 0.15 mg (White Label, EpiPen Jr.). Both strengths deliver a single dose. Sometimes a single dose of epinephrine may not be enough to completely reverse the effects of an anaphylactic reaction; for that reason, some physicians prescribe more than one auto-injector Also, some patients like to keep one unit at home, one on their person, and one at their place of work to ensure that an EpiPen® Auto-Injector is available at all times.

10. How and where can I obtain an EpiPen® Auto-Injector?

See your physician first, since a prescription is required. EpiPen® and EpiPen® Jr. Auto-Injectors are available from most pharmacies. Once you have purchased an EpiPen, be sure to register it using the "Expiration Alert" coupon on the package insert. You will be notified prior to the expiration date of your unit. Complete directions for use are included with every EpiPen® Auto-Injector. If your doctor prescribes the EpiPen® Auto-Injector for you, periodically study the

directions carefully so that you will be prepared for future emergencies.

11. Are there any special tips or precautions I should know?

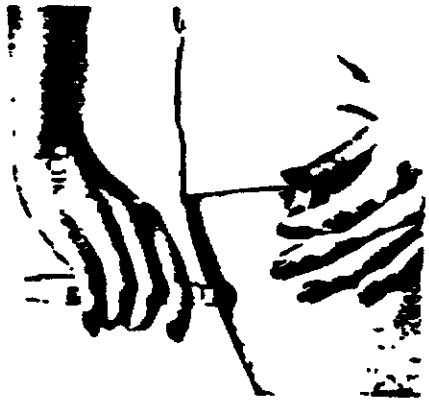
The EpiPen® Auto-Injector is quite durable, but like any instrument it can be damaged if mishandled. Remove the gray safety cap only when you are ready to use the EpiPen, otherwise the unit could be activated prematurely. Never put your fingers over the black tip when removing the safety cap, or after the safety cap has been removed. Epinephrine is stable at room temperature until the marked expiration date. EpiPen should not be refrigerated; refrigeration for extended periods may cause the unit to malfunction. Neither should the EpiPen® Auto-Injector be exposed to extreme heat, such as in the glove compartment or trunk of a car during the summer. Do not expose your auto-injector to direct sunlight; light and heat can cause epinephrine to oxidize and go bad, turning brown. Check contents of the glass cartridge in the EpiPen periodically through the viewing window of the unit to make sure the solution is clear and colorless. If solution appears brown, replace the unit immediately. Always replace your Epipen with a fresh unit prior to the expiration date.

12. After using an EpiPen® Auto-Injector, what else must I do?

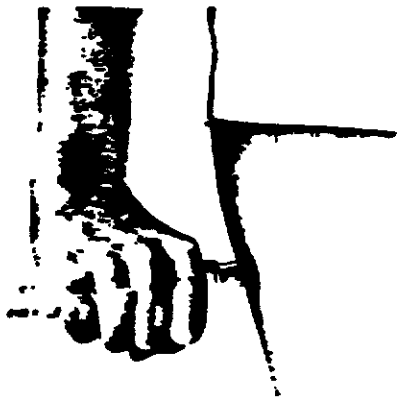
The EpiPen® Auto-Injector is intended for emergency use only. After use, you should try to get further medical help immediately. At the same time, try to keep warm and avoid unnecessary exertion. The effects of the injection begin to wear off after 10 to 20 minutes, therefore it is important that you seek further medical assistance. Make certain you tell the health professionals who will treat you that you have given yourself an injection of epinephrine.

How to use the EpiPen® Auto-Injector... Three simple steps:

1. Pull off gray safety cap



2. Place black tip on outer thigh



3. Push EpiPen Auto-Injector against thigh until unit activates, and hold in place several seconds. Then discard unit

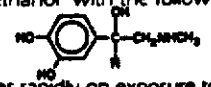
EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0.3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP 1:1000 (0.3 mL)

DESCRIPTION

The EpiPen Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection USP 1:1000 (0.3 mL) in a sterile solution. For stability purposes, approximately 1.7 mL remains in the auto-injector after activation. Each 0.3 mL contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5-5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is R-(3, 4-dihydroxyphenyl)-a-methylaminoethanol with the following structure:



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema. The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15°-30°C/59°-86°F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. Select an appropriate injection site such as the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, advise the patient to go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the anterolateral aspect of the thigh.

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and

exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used It must be clearly determined that the patient is at risk of future anaphylaxis since the following risks may be associated with epinephrine administration (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias, e g , digitalis, mercurial diuretics, or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors

Hyperthyroid individuals individuals with cardiovascular disease hypertension or diabetes elderly individuals pregnant women, and children under 30 kg (66 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis Therefore patients with these conditions and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration).

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness tremor, headache, apprehension nervousness and anxiety

Cardiac arrhythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis in detail the patient instructions and operation of the EpiPen Auto-Injector Inject the delivered dose of the EpiPen Auto-Injector (0 3 mL Epinephrine Injection USP 1 1000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary See detailed Directions for Use on the accompanying Patient Instructions

Usual epinephrine adult dose for allergic emergencies is 0 3 mg For pediatric use, the appropriate dosage may be 0 15 or 0 30 mg depending upon the body weight of the patient (see labeling for EpiPen Jr) However the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children

With severe persistent anaphylaxis repeat injections with an additional EpiPen may be necessary

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection, USP 1 1000, 0 3 mL) are available singly or in packages of twelve (pharmacy pack), NDC 0268-0301-01 Store in a dark place at room temperature (15°-30°C/59°-86°F) Do not refrigerate

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC.
35 CHANNEL DRIVE, PORT WASHINGTON, NY 11050, U.S.A.
By Survival Technology, Inc., Bethesda, MD 20814, U.S.A

[redacted]

File EP Update Book

MAR 05 1990

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 2, 1990

CONFIDENTIAL

Gary W. Leyland
Director
Clinical and Regulatory Affairs
Survival Technology, Inc
8101 Glenbrook Road
Bethesda, Maryland 20814

Dear Mr Leyland:

This will respond to your submission of proposed advertising material for your prescription drug Epipen (epinephrine) Auto-Injector, #19-430 and our telephone conversation of March 1, 1990.

The proposed material represents labeling for your product and will be referred to as promotional labeling to avoid confusion with the "approved" labeling. The promotional labeling is intended to be used as a patient aid for your product and is set up in a "Question/Answer" format. Following our earlier discussion about the material, some modifications have been incorporated into this new submission as outlined in you cover letter dated 2/27/90.

The material, as promotional labeling (labeling), must be consistent with and not contrary to the approved labeling. In addition, the material must include information about the drug (i.e. disclosure) in the same language and emphasis as the approved labeling. These principles were discussed with you and apparently were understood. Some repetition of these concepts may appear below, it is only intended to preclude any confusion or answer other questions which may arise.

Review of this revised material has been completed. The following recommendations are made to ensure communication of information that meets the requirements of this type of material. We request that you take the following action:

1) Q/A #6-Please add some emphasis to the additional statement about *not administering the Epipen either into a vein or in the buttocks.* The labeling uses capitals, but you may use bold faced type, italics or any method that adds some special emphasis to these ideas.

2) Please add some connecting phrase to link the "Q/A" portion with *the added "full product information." In professional use only* material, our concern for this "link" would be less. However, as a consumer aid every effort to help the patient use the auto-injector correctly will produce a reliable source to supplement the physicians counseling throughout the products "shelf life."

CONFIDENTIAL

With the above modifications and as mentioned on 3/1/90, the promotional labeling will be regarded as acceptable.

Aside from the comments provided, additional objections were not noted in the material reviewed. Changes to the material are your responsibility. If at a subsequent time, the FDA changes its opinion, you will be notified and given a reasonable time for correction before further action is taken. This notification that a particular advertising piece is objectionable shall be in written form. We trust these comments are helpful. Contact our office if we may be of further assistance.

Sincerely yours,

William V. Purvis
Assistant to the Director
Division of Drug Advertising
and Labeling
Office of Drug Standards

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS FOR HUMAN USE

1. DATE SUBMITTED: 9/9/91

Form Approved OMB No 0910-0001
Expiration Date, May 31, 1986

2 NDA NO: N 19430

NOTE This form is required by law (21 CFR 314.81) Failure to report can result in withdrawal of approval of NDA or Antibiotic Application

CONFIDENTIAL

INSTRUCTIONS
1 Submit a separate form (parts 1 through 3) for each NDA or Antibiotic Application for which advertisement or promotional labeling material is submitted
2 Attach two copies of each piece of material to the form
3 Enter in Column C the total number of types *(not copies)* of material submitted
4 Forward form and attachments to Department of Health and Human Services, Food and Drug Administration (HFN-240), 5600 Fishers Lane, Rockville, Maryland 20857

3 APPLICANT	4 DRUG NAME
Survival Technology, Inc.	EpiPen®Auto-Injector

5 ADVERTISEMENT/PROMOTIONAL LABELING MATERIAL

TYPE a	DATE OF ISSUANCE b	NO c	IDENTIFICATION (Use code or other designation If necessary, continue on 8½ x 11) d
JOURNAL ADVERTISEMENT(S)			
PROMOTIONAL LABELING			
BROCHURE(S) LEAFLET(S)	4/91	1	4 Page Color Brochure
FILE CARD(S)			
HOUSE ORGAN(S)			
PRICE LIST(S)			
PHYSICIANS SAMPLE(S)			
PROMOTIONAL LETTER(S)			
LITERATURE REPRINT(S)			
OTHER (Audio-Visual material (films, tapes, etc.) or typed scripts of such material).			
LABELING ON WHICH THE ABOVE IS BASED (Include currently approved labeling with each submission)			
PACKAGE INSERT(S)	11/88	1 ea.	Physician and Patient Inserts
OTHER LABELING (If no package insert(s) exists)			

6. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Gary W. Leyland
Director, Regulatory Affairs

7 SIGNATURE

8 APPLICANTS RETURN ADDRESS (Begin typing address directly below window dot)

Survival Technology, Inc.
ATTN: Gary W. Leyland
8101 Glenbrook Road
Bethesda, MD 20814

9 FDA ACKNOWLEDGEMENT

FORM FDA 2253 (5/85) PREVIOUS EDITION IS OBSOLETE

MERIDIAN
01659

CONFIDENTIAL

PHYSICIAN INSERT

(PHARMACIST - PLEASE REMOVE BEFORE DISPENSING)

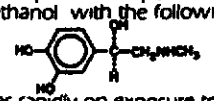
EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0 3 mg intramuscular dose of epinephrine from Epinephrine Injection, USP, 1 1000 (0 3 mL)

DESCRIPTION

The EpiPen Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use Each EpiPen Auto-Injector delivers a single dose of 0 3 mg epinephrine from Epinephrine Injection, USP, 1 1000 (0 3 mL) in a sterile solution For stability purposes, approximately 1 7 mL remains in the auto-injector after activation Each 0 3 mL contains 0 3 mg epinephrine, 1 8 mg sodium chloride 0 5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection The pH range is 2 5-5 0

Epinephrine is a sympathomimetic catecholamine Chemically epinephrine is B-[3, 4-dihydroxyphenyl)-a-methylaminoethanol with the following structure



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin EpiPen Auto-Injectors whose contents show evidence of discoloration should be replaced

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided Store at room temperature (15°-30°C/59°-86°F) Do not refrigerate Before using, check to make sure solution in Auto-Injector is not discolored Replace the Auto-Injector if the solution is discolored or contains a precipitate Avoid possible inadvertent intravascular administration Select an appropriate injection site such as the thigh DO NOT INJECT INTO BUTTOCK

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure DO NOT INJECT INTRAVENOUSLY Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons The alternatives to using epinephrine in a life-threatening situation may not be satisfactory The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided If there is an accidental injection into these areas, advise the patient to go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the anterolateral aspect of the thigh

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and

exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used It must be clearly determined that the patient is at risk of future anaphylaxis since the following risks may be associated with epinephrine administration (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias e g digitalis mercurial diuretics or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors

Hyperthyroid individuals individuals with cardiovascular disease hypertension or diabetes elderly individuals, pregnant women and children under 30 kg (66 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration

Despite these concerns epinephrine is essential for the treatment of anaphylaxis Therefore patients with these conditions and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration)

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety

Cardiac arrhythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis, in detail the patient instructions and operation of the EpiPen Auto-Injector Inject the delivered dose of the EpiPen Auto-Injector (0 3 mL Epinephrine Injection USP 1 1000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary See detailed Directions for Use on the accompanying Patient Instructions

Usual epinephrine adult dose for allergic emergencies is 0 3 mg For pediatric use the appropriate dosage may be 0 15 or 0 30 mg depending upon the body weight of the patient (see labeling for EpiPen Jr) However the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children

With severe persistent anaphylaxis, repeat injections with an additional EpiPen may be necessary

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present

HOW SUPPLIED

EpiPen Auto-Injectors (Epinephrine Injection USP 1 1000, 0 3 mL) are available singly or in packages of twelve (pharmacy pack) NDC 0268-0301-01 Store in a dark place at room temperature (15°-30°C/59°-86°F) Do not refrigerate

CAUTION: Federal (U S A) law prohibits dispensing without a prescription

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC.
35 CHANNEL DRIVE, PORT WASHINGTON, NY 11050, U.S.A.
By Survival Technology, Inc , Bethesda, MD 20814 U S A

Date of Issue November, 1988

1928

PATIENT INSERT

(PHARMACIST - PLEASE DISPENSE WITH PRODUCT)

CONFIDENTIAL

0.3 mg

NDC 0268-0301-01
DIN 509558
NSN 6505-01-152-7626

READ INSTRUCTIONS CAREFULLY, BEFORE AN EMERGENCY ARISES

EpiPen®

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.3 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION USP 1:1000 (0.3mL)

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C/59°-86°F). DO NOT REFRIGERATE.

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC., PORT WASHINGTON, NY 11050 U.S.A.
by Survival Technology Inc. Bethesda MD 20814 U.S.A.
US Patent No. 3 882 863 4 031 893 and 3 712 301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.
IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Auto-Injector should be used only by a hypersensitive (allergic) person in an allergic emergency as prescribed by a physician. Such emergencies may occur from insect stings or bites, foods, drugs or other allergens, as well as idiopathic or exercise-induced anaphylaxis.

THE EPIPEN® AUTO-INJECTOR

The EpiPen Auto-Injector is a disposable, prefilled *automatic injection device which is designed to deliver a* single dose of 0.3 mg of epinephrine.

- Keep the EpiPen Auto-Injector ready for use at all times.
- Protect from exposure to light and extreme heat.
- Note the expiration date on the unit and replace it prior to expiration.
- Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Auto-Injector is designed with a see-through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone *treatment*.

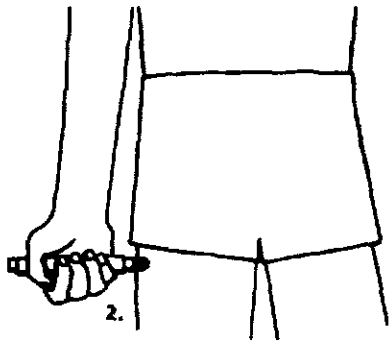
EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

If you experience the signs and symptoms described by your physician use the EpiPen Auto-Injector im*mediately, through clothing if necessary. If you have* been stung by an insect, remove the insect's stinger *with your fingernails if possible; do not squeeze,* pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN AUTO-INJECTOR

1. Pull off gray safety cap (illustration 1).
2. *Place* black tip on thigh at *right angle* to leg (illustration 2). (Always apply to *thigh.*)
3. Press hard into thigh until Auto-*Injector mechanism functions, and* hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



SEE OTHER SIDE FOR ADDITIONAL INFORMATION ABOUT INSECT STINGS.

MERIDIAN
01662

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
CENTER LABORATORIES
EPIPEN ALERT
35 CHANNEL DRIVE
PORT WASHINGTON, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____
(Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

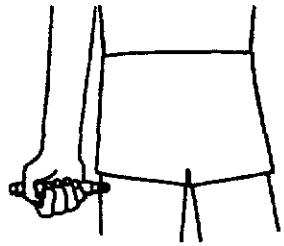
CITY _____ STATE _____ ZIP _____

CONFIDENTIAL

Tear off here and mail to address shown at bottom

WARNING

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the thigh as indicated in the drawing below.



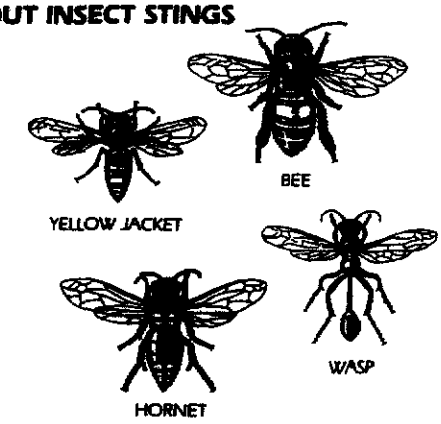
ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

STINGING INSECTS: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.

SUGGESTIONS FOR AVOIDANCE OF INSECT STINGS

OUTDOORS: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

PERSONAL: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints, or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.



Date of Issue November 1988

1948

PHYSICIAN INSERT

(PHARMACIST - PLEASE REMOVE BEFORE DISPENSING)

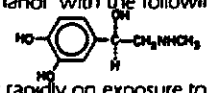
EPIPEN® JR. 0.15 mg EPINEPHRINE AUTO-INJECTOR

Auto-Injector for Intramuscular Injection of Epinephrine
For the Emergency Treatment of Allergic Reactions (Anaphylaxis)
Delivers 0 15 mg intramuscular dose of epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL)

DESCRIPTION

The EpiPen Jr Auto-Injector contains 2 mL Epinephrine Injection for emergency intramuscular use Each EpiPen Jr Auto-Injector delivers a single dose of 0 15 mg epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL) in a sterile solution For stability purposes approximately 1 7 mL remains in the auto-injector after activation Each 0 3 mL contains 0 15 mg epinephrine 1 8 mg sodium chloride 0 5 mg sodium metabisulfite hydrochloric acid to adjust pH and Water for Injection The pH range is 2 5-5 0.

Epinephrine is a sympathomimetic catecholamine Chemically epinephrine is 8-(3 4-dihydroxyphenyl)-a-methylaminoethanol with the following structure



It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin EpiPen Jr Auto-Injectors whose contents show evidence of discoloration should be replaced

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites foods drugs, and other allergens It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea Epinephrine also alleviates pruritis urticaria and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites foods drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis The EpiPen Jr Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope tachycardia thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes urticaria or angioedema The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided Store at room temperature (15°-30°C/59°-86°F) Do not refrigerate Before using, check to make sure solution in Auto-Injector is not discolored Replace the Auto-Injector if the solution is discolored or contains a precipitate Avoid possible inadvertent intravascular administration Select an appropriate injection site such as the thigh DO NOT INJECT INTO BUTTOCK

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure DO NOT INJECT INTRAVENOUSLY Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons The alternatives to using epinephrine in a life-threatening situation may not be satisfactory The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided If there is an accidental injection into these areas advise the patient to go immediately to the nearest emergency room for treatment EpiPen should **only** be injected into the anterolateral aspect of the thigh

PRECAUTIONS

Epinephrine is essential for the treatment of anaphylaxis Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites foods drugs and other allergens as well as idiopathic and

exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used It must be clearly determined that the patient is at risk of future anaphylaxis since the following risks may be associated with epinephrine administration (See Dosage and Administration)

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias e g digitalis, mercurial diuretics, or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors

Hyperthyroid individuals individuals with cardiovascular disease hypertension, or diabetes elderly individuals pregnant women and children under 15 kg (33 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis Therefore patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE and as indicated under PRECAUTIONS above

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration)

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor dizziness weakness tremor headache apprehension, nervousness and anxiety

Cardiac arrhythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

A physician who prescribes EpiPen Jr should take appropriate steps to insure that the patient understands the indications and use of this device thoroughly The physician should review with the patient or any other person who might be in a position to administer EpiPen Jr to a patient experiencing anaphylaxis in detail the patient instructions and operation of the EpiPen Jr Auto-Injector Inject the delivered dose of the EpiPen Jr Auto-Injector (0 3 mL Epinephrine Injection USP 1 2000) intramuscularly into the anterolateral aspect of the thigh through clothing if necessary See detailed Directions for Use on the accompanying Patient Instructions

Usual epinephrine adult dose for allergic emergencies is 0 3 mg For pediatric use the appropriate dosage may be 0 15 or 0 30 mg depending upon the body weight of the patient (0 01 mg/kg body weight) However the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed The physician should consider using other forms of injectable epinephrine if lower doses are felt to be necessary for small children

With severe persistent anaphylaxis repeat injections with an additional EpiPen Jr may be necessary

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present

HOW SUPPLIED

EpiPen Jr Auto-Injectors (Epinephrine Injection USP 1 2000 0 3 mL) are available singly or in packages of twelve (pharmacy pack) NDC 0268-0302-1 Store in a dark place at room temperature (15°-30° C/59°-86°F) Do not refrigerate

CAUTION: Federal (U.S A) law prohibits dispensing without a prescription

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC.
35 CHANNEL DRIVE, PORT WASHINGTON, NY 11050, U.S.A. Date of Issue November 1988
By Survival Technology Inc Bethesda MD 20814 U S A

1938

PATIENT INSERT

(PHARMACIST - PLEASE DISPENSE WITH PRODUCT)

NDC 0268-0302-01
DIN 578657

READ INSTRUCTIONS CAREFULLY, BEFORE AN EMERGENCY ARISES

EpiPen® Jr.

EPINEPHRINE AUTO-INJECTOR

FOR ALLERGIC EMERGENCIES (ANAPHYLAXIS)

DELIVERS 0.15 mg INTRAMUSCULAR DOSE OF EPINEPHRINE FROM EPINEPHRINE INJECTION USP 1:2000 (0.3mL)

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription

REPLACE IF DISCOLORED. STORE IN A DARK PLACE AT ROOM TEMPERATURE (15°-30°C/59°-86°F). DO NOT REFRIGERATE.

MANUFACTURED FOR CENTER LABORATORIES, DIVISION OF EM PHARMACEUTICALS, INC
PORT WASHINGTON, NY 11050 U.S.A.
by Survival Technology Inc. Bethesda MD 20814 U.S.A.
US Patent No. 3,882,863; 4,031,893 and 3,712,301

TO THE PATIENT:

READ THESE INSTRUCTIONS CAREFULLY BEFORE AN EMERGENCY ARISES.
IMPORTANT: DO NOT REMOVE SAFETY CAP UNTIL READY FOR USE.

This unit is an automatic injection device containing epinephrine for allergic emergencies. The EpiPen Jr. Auto-Injector should be used only by a hypersensitive (allergic) person in the event of an allergic emergency as prescribed by a physician. Such emergencies may occur from insect stings or bites, foods, drugs or other allergens as well as idiopathic or exercise-induced anaphylaxis.

THE EPIPEN® JR. AUTO-INJECTOR

The EpiPen Jr. Auto-Injector is a disposable prefilled automatic injection device which is designed to deliver a single dose of 0.15 mg of epinephrine.

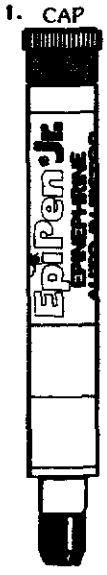
- Keep the EpiPen Jr. Auto-Injector ready for use at all times.
- Protect from exposure to light and extreme heat.
- Note the expiration date on the unit and replace it prior to expiration.
- Replace any auto-injector if the solution is discolored or contains a precipitate. The EpiPen Jr. Auto-Injector is designed with a see-through window to allow periodic examination of its contents. The physician may recommend emergency use of an auto-injector with discolored contents rather than to postpone treatment.

EMERGENCY TREATMENT OF ALLERGIC REACTION/ANAPHYLAXIS

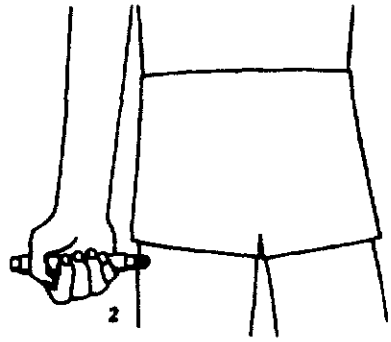
If you experience the signs and symptoms described by your physician, use the EpiPen Jr. Auto-Injector immediately through clothing if necessary. If you have been stung by an insect, remove the insect's stinger with your fingernails if possible; do not squeeze, pinch or push it deeper into the skin. If available, ice packs or sodium bicarbonate soaks may then be applied to the area stung. Keep warm and avoid exertion.

NOTIFY YOUR DOCTOR IMMEDIATELY OR REPORT TO THE NEAREST HOSPITAL. If you have used EpiPen Jr., be sure to explain to the physician that you have received an intramuscular injection of epinephrine.

DIRECTIONS FOR USING EPIPEN JR. AUTO-INJECTOR



1. Pull off gray safety cap (Illustration 1).
2. Place black tip on thigh at right angle to leg (Illustration 2). (Always apply to thigh.)
3. Press hard into thigh until Auto-Injector mechanism functions and hold in place for several seconds. The EpiPen unit should then be removed and discarded. Massage the injection area for 10 seconds.



SEE OTHER SIDE FOR ADDITIONAL INFORMATION ABOUT INSECT STINGS.

EPIPEN® AUTO-INJECTOR EXPIRATION ALERT

It is recommended that your EpiPen® Auto-Injector be replaced prior to the expiration date shown on the label. For your safety and convenience, Center Laboratories offers an Alert Service. We will notify you by mail when it is time to replace this unit. Just fill out the form, tear it off and return to us.

MAIL TO:
CENTER LABORATORIES
EPIPEN ALERT
35 CHANNEL DRIVE
PORT WASHINGTON, N.Y. 11050
U.S.A.

Expiration date _____ Lot No _____

NAME OF PURCHASER _____
(Please Print)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

DATE OF PURCHASE _____

I purchased my EpiPen® Auto-Injector at

PHARMACY NAME _____

ADDRESS _____

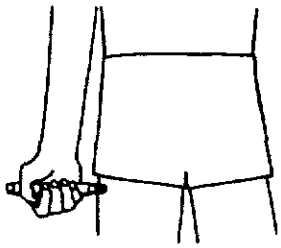
CITY _____ STATE _____ ZIP _____

Tear off here and mail to address shown at bottom

CONFIDENTIAL

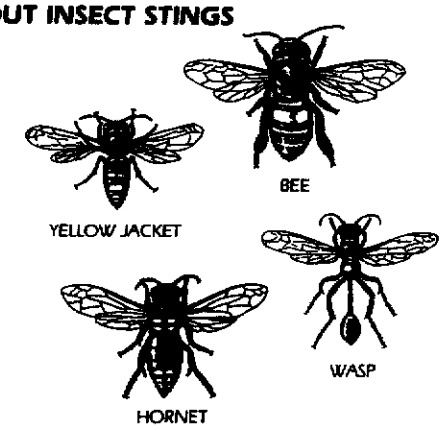
WARNING

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. EpiPen should **only** be injected into the thigh as indicated in the drawing below.



ADDITIONAL PATIENT INFORMATION ABOUT INSECT STINGS

STINGING INSECTS: The principal stinging insect offenders belong to a group of insects called Hymenoptera. They are the yellow jacket, the honeybee, the wasp, and the hornet. These insects are widely distributed throughout the world.



SUGGESTIONS FOR AVOIDANCE OF INSECT STINGS

OUTDOORS: Food attracts insects. Keep food in covered containers. Keep garbage containers covered and avoid open garbage receptacles.

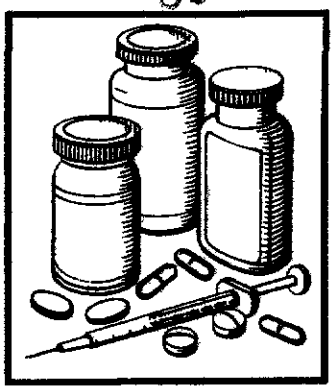
PERSONAL: Avoid using strong perfumes found in hair sprays, hair tonics, suntan lotions and other cosmetics. Avoid wearing brightly colored clothing, flowery prints or black, as this color seems to attract insects more than white, green, tan, or khaki garments. Wear shoes at all times when out of doors. If possible, keep arms and legs covered by garments.

Date of Issue: November 1988

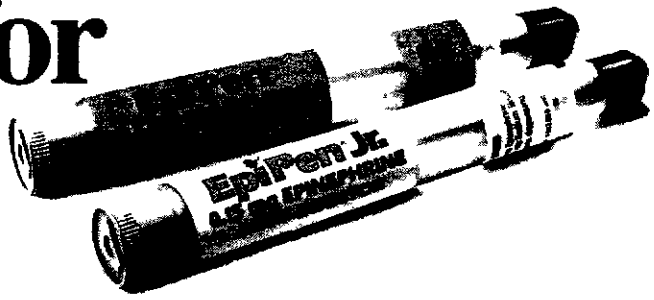
195B

MERIDIAN
01667

The only AUTOMATIC Epinephrine Delivery System

Now any allergic emergency is an indication for



EpiPen®

Epinephrine Auto-Injectors

MERIDIAN
01668

CONFIDENTIAL

Center Laboratories
Division of EM Industries, Inc
35 Channel Drive, Port Washington, NY 11050
Tel 800-2-CENTER or 516-767-1800

Manufactured for Center Laboratories by
Survival Technology, Inc , Bethesda, MD 20814
U S Patent Nos 3,882,863, 4,031,893 and 3 712,301

Brief summary: Before prescribing, please consult package insert for complete product information

DESCRIPTION

*The EpiPen Auto-Injectors contain 2 mL Epinephrine Injection for emergency intramuscular use Each EpiPen Auto-*Injector delivers a single dose of 0 3 mg epinephrine from Epinephrine Injection USP 1 1000 (0 3 mL) in a sterile solution Each EpiPen Jr Auto-Injector delivers a single dose of 0 15 mg epinephrine from Epinephrine Injection USP 1 2000 (0 3 mL) in a sterile solution Each 0 3 mL also contains 1 8 mg sodium chloride 0 5 mg sodium metabisulfite hydrochloric acid to adjust pH, and Water for Injection The pH range is 2 5-5 0

CLINICAL PHARMACOLOGY

Epinephrine is a sympathomimetic drug acting on both alpha and beta receptors It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs and other allergens It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action

INDICATIONS AND USAGE

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites foods drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia thready or unobtainable pulse associated with a fall in blood pressure convulsions, vomiting diarrhea and abdominal cramps involuntary voiding, wheezing dyspnea due to laryngeal spasm pruritis, rashes urticaria or angioedema The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation

WARNINGS

Epinephrine is light sensitive and should be stored in the tube provided Store at room temperature (15°-30°C/59°-86°F) Do not refrigerate Before using check to make sure solution in Auto-Injector is not discolored Replace the Auto-Injector if the solution is discolored or contains a precipitate Avoid possible inadvertent intravascular administration Select an appropriate injection site such as the thigh DO NOT INJECT INTO BUTTOCK Large doses or *accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure* DO NOT INJECT INTRAVENOUSLY Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite a sulfite that may in other products cause allergic-type reactions including anaphylactic *symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons The alternatives to* using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided If there is an accidental injection into these areas, advise the patient to go immediately to the nearest *emergency room for treatment EpiPen should ONLY be injected into the anterolateral aspect of the thigh*

PRECAUTIONS

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease Use of epinephrine with drugs that may sensitize the heart to arrhythmias, e g digitalis mercurial diuretics or quinidine ordinarily is not recommended Anginal pain may be induced by epinephrine in patients with coronary insufficiency The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors Hyperthyroid individuals individuals with cardiovascular disease hypertension or diabetes elderly individuals pregnant women and children under 30 kg (66 lbs) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration Despite these concerns epinephrine is essential for the treatment of anaphylaxis. Therefore patients with these conditions and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used

CARCINOGENESIS MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted

USAGE IN PREGNANCY

Pregnancy Category C Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose There are no adequate and well-controlled studies in pregnant women Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

PEDIATRIC USE

Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration)

ADVERSE REACTIONS

Side effects of epinephrine may include palpitations tachycardia sweating nausea and vomiting respiratory difficulty, pallor dizziness weakness tremor headache apprehension nervousness and anxiety

Cardiac arrythmias may follow administration of epinephrine

OVERDOSAGE

Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation

DOSAGE AND ADMINISTRATION

Usual epinephrine adult dose for allergic emergencies is 0 3 mg For pediatric use the appropriate dosage may be 0 15 or 0 30 mg depending upon the body weight of the patient. However, the prescribing physician has the option of prescribing more or less than these amounts based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed With severe persistent anaphylaxis repeat injections with an additional EpiPen may be necessary

HOW SUPPLIED

EpiPen and EpiPen Jr Auto-Injectors are available singly or in packages of twelve

CAUTION

Federal (U S A) law prohibits dispensing without a prescription

Issued April 1991

MERIDIAN
01669

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 231 PT WASHINGTON NY

POSTAGE WILL BE PAID BY ADDRESSEE

CENTER LABORATORIES
P.O. Box 70
Port Washington, N Y. 11050

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES